Endocrinology

The Bulletin *of the*
Association *for the* Study *of*
Internal Secretions

March-April, 1927

STUDIES ON VIGOR
XVI. ENDOCRINE FACTORS IN VIGOR*†

R. G. HOSKINS

From the Department of Physiology, the Ohio State University
COLUMBUS

During the past three years various members of the Physiology Department of the Ohio State University have been engaged in a series of investigations on the various factors that serve to modify the vigor of the individual. The method (1) is to confine albino rats in small housing cages having uninterrupted access to revolving cylinders in which they can exercise *ad libitum*. The revolutions are automatically recorded by ratchet counters. Observations upon hundreds of individuals have shown that so large a part of the total energy expenditure goes to running in the wheels that a record of the revolutions of these serves as a rather accurate criterion of the animal's tendency to exercise, hence, presumably, of its general vigor.

The activity of rats thus determined is notably variable, both as regards the individual and as regards large groups. It was

* Aided by a grant from the Bache Fund.

† Presidential address read before the Eleventh Annual Meeting of the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

assumed in the beginning that if a sufficient number of individual determinations was made the record of total colony revolutions per day would be fairly constant. Such, however, is not the case. On some days most of the animals are relatively active, and on other days some degree of depression is seen. Attempts have been made to correlate these differences with a variety of meteorological factors, such as temperature, barometric pressure, wind velocity and direction, luminosity, humidity, and diurnal variations of temperature. No simple relationship has been discovered. The methods of partial correlation, however, have not been adequately applied.

Another finding that was not anticipated, considering the uniformity of heredity and environment, is that there is marked variation in the spontaneous activity of litter-mates, even though all are apparently equally healthy and alert. In a few cases autopsy studies have been made of the endocrine gland weights of high and of low activity animals. There is a suggestion that high activity may be correlated with large thyroids, sex glands and adrenals, but the data so far secured are not consistent nor adequate.

THE PINEAL

No successful studies have as yet been made on the pineal gland.

THE HYPOPHYSIS

A few clinical observations have given the impression that "pituitrin" is of some benefit in cases of asthenia in the human subject. To a few rats showing low activity this extract was administered subcutaneously in 0.1 or 0.2 cc. doses, daily. No improvement in activity was seen. No other experiments directly involving the hypophysis have been made.

THE THYROID

It was confidently expected, in view of its well-known effect on basal metabolism that thyroid deficiency would materially reduce the spontaneous activity. This operation, however, in some 25 rats, has had little or no effect. Careful autopsies indicate that the tissue of the thyroid gland, proper, in nearly all cases had been completely removed. Whether undiscovered bits of

thyroid tissue were left behind in sufficient amount to maintain an adequate supply of secretion or whether compensation occurred in other glands has not been determined. The details on 20 of these animals will be reported by Van Buskirk and Lee.

That thyroid extract has a general "tonic" effect has been claimed by some clinicians and denied by others. As a test of the theory, desiccated thyroid gland substance was administered to 11 senile animals in dosage of 0.1 grain three times a week to 1 grain six times a week. The effects were either negative or depressant. Similar experiments in castrated animals showing marked deficiency in spontaneous activity gave, likewise, negative results. In two cases thyroid substance was administered to rats from which the thyroids and parathyroids had been reremoved. In view of the negative result from thyroidectomy, it is not surprising that no increased activity was seen. Whether as coincidence, or otherwise, these two thyroidectomized animals seemed especially susceptible to the toxic influence of the drug and showed a marked decrease in activity.

THE PARATHYROIDS

Results of parathyroidectomy in the animals that survived operation have been consistently negative so far as spontaneous activity is concerned.

THE ADRENALS

Since the old experiments of Phillipeau and of Hartley it has been widely assumed that adrenal extirpation has no influence on the vital processes of the rat. This anomaly has been explained on the grounds that the animal is rather abundantly supplied with accessory adrenal tissue. It is true that after ablation of both glands the rat seems normally alert and active. Durrant (2) has shown, however, that in a considerable proportion of cases the rats, when placed in recording cages, show a marked degree of chronic adynamia. In the animals that recover normal activity, hypertrophied cortical rests near the site of the glands, proper, were ordinarily found.

Gans and Miley (3) have made ergographic studies on 22 rats from which both adrenals had been removed within a period of 1 to 8 days, as well as on control animals. It was found that, although the absolute strength of the gastrocnemius mus-

cles was essentially the same in both groups, the rats lacking adrenals showed much greater fatigability and were capable of giving, on the average only 1/16 as much work as were their controls before complete fatigue set in.

Rats showing chronic adynamia after adrenal extirpation would seem to be particularly favorable subjects for studies on experimental therapeutics. A somewhat extensive series of such studies was made by Durrant and the writer. In brief, it was found that glycerine extracts of whole adrenal gland could not be administered hypodermically without causing serious ulceration and marked impairment of activity. No improvement of activity was seen with smaller doses given by mouth, and larger doses killed the animals. Surmising that the deleterious effects might be due to the contained adrenalin, the experiments were repeated with glycerine extract of cortex, only, fed by mouth. In no case, however, was any convincing evidence obtained that such extracts are of benefit.*

THE PANCREAS

No experiments have been made either by extirpation or by administering insulin.

THE OVARIES

The observations of Wang (4) that extirpation of the ovaries markedly reduces the spontaneous activity of the rat was readily confirmed. How the reduction is brought about, however, offers a somewhat difficult problem. An approach to its solution has been made by Miley (5), who studied the incidence of fatigue in the gastrocnemius muscles of normal and of spayed rats stimulated in situ by faradizing the sciatic nerves. It was found that the absolute strength of the muscles, gram for gram, was 40 per cent greater in the control than in the experimental animals, and the total amount of work elicitable before complete fatigue was only 33.6 per cent as great in the spayed rats as in the controls. These results obviously carry the problem only one stage further. Whether the adynamia is due to interference with the metabolism of the muscle or its innervation, or to failure of supporting bodily functions, such as respiration, circulation, sugar supply, or what not, remains to be determined.

* We are indebted to Armour & Co., Chicago, and to Mr. Frederick Fenger of this firm for generous supplies of material.

Attempts to restore the vigor of spayed animals by the administration of ovarian products have been so far without success, although Wang has shown that this can be accomplished handily by means of ovarian grafts. In view of the claims of Hancher and Rogers that marked improvement was obtained in clinical cases from the oral administration of glycerine extracts of ovary, it was hoped that such would prove efficacious under exactly controlled experimental conditions (revolving cage method). In the hands of Durrant (1) the method gave completely negative results.

Similarly negative results were obtained from subcutaneous injections of aqueous extracts of corpus luteum, using Hynson, Westcott and Dunning and Eli Lilly commercial products (Durrant, 6). That the corpus luteum extracts were not entirely inert, however, is indicated by the fact that animals to which they were administered showed considerable loss of fertility.

In view of the fact that the energizing effect of the ovary is presumably due to hormone factors and of the claims by certain clinicians that hysterectomy causes ovarian depression, Durrant (7) investigated the effect of this operation on vigor. The results in this case, also, were negative.

THE TESTES AND PROSTATE

That castration results in some degree of loss of aggressiveness has long been recognized. In accordance with this fact it was found that castrated rats kept in the recording cages showed a marked reduction in spontaneous activity (8). When the operation was performed at the early adult period the activity was cut down five fold. When, however, the operation was performed within the first 12 days of life, Gans (9) showed in 25 rats that no reduction in activity was brought about. No evidence has been secured as to what sort of compensating changes take place to prevent the loss of vigor under these conditions. The same investigator (10) has secured data on 10 animals to indicate that loss of one testis is without effect, but that with only a half testis left in situ the activity is cut down some 25 per cent. Removal of still larger proportions of the testis tissue results in still greater decrements of activity. This series should be further extended.

Gans and Hoskins (11) made ergographic studies on 15 castrated rats showing marked degrees of loss of spontaneous activity. It was found that, although the absolute strength of the gastrocnemii was as great in the castrates as the controls, fatigue supervened more quickly and the total work elicitable under repeated stimulations was only 64 per cent of that of the controls. The underlying cause of the increased fatigability has not been determined.

We have had many opportunities to confirm Slonaker's observation that senile rats show greatly decreased activity. To what extent the loss of sex hormones accounts for this lethargy is not known.

During the past two years many attempts have been made to restore the vigor of castrated and senile animals by testis grafts. One series of studies giving completely negative results has already been reported. A repetition of the grafting experiments was carried out in some 40 other animals. Here, again, negative results were secured in all castrates and all but two senile animals. In these two, single grafts of testes from rats 10-12 days old affixed directly to the testes of the hosts was followed by a consistent though not extensive increase in activity that persisted three or four months.

In practically all cases studied in our completed series, entire resorption of the grafts has taken place. Since other observers have reported frequent "takes" in the rat, and since our own technic has been carefully carried out, we have been led to suspect that the activity in the recording wheels may have prevented any significant persistence of the grafts.

Smith (13) has recently shown in case of the hypophysis that, although single grafts are without perceptible influence, daily repetition of the grafting leads to marked physiological effects. In collaboration with Boukalik another series of experiments is being carried out on castrates and senile animals. The testis material has been secured from rats about 120 grams in weight and implanted by the Stanley syringe method in various loci—under the skin along the ventral wall and in the scrotum. At first 0.1 to 0.2 cc. was implanted three times, then six times a week. In two instances some apparently significant increase in activity was seen within a few days. The experiments are being continued with larger amounts of gland substance.

In collaboration with J. B. Brown and Milton O. Lee an extensive series of experiments (not hitherto reported) was carried out on the effects of feeding desiccated testis and of subcutaneous injections of a variety of testis extracts. These latter included saline, glycerine and lipoid-solvent extracts (Allen and Doisy method) and dialysates of various sorts (distilled water, saline, weak acid and alcohol). Without going into laborious detail, suffice it to say that no significant increase on activity was seen in any case.

Lee has made similar experiments with a saline extract of prostate gland supplied by the Eli Lilly Co. The results in this series, also, were negative.

The possibility has occurred to us, and has been suggested by various investigators with whom the work has been discussed, that simultaneous administration of prostatic and testis extracts might give better results. Opportunity has not been had, as yet, to test the possibility.

Vasectomy in senile animals has consistently failed to give any improvement in apparent vigor.

Whether the ovaries or the testes afford a more potent energizing hormone offers an interesting question. Since both sexes are reduced to a similar state of lethargy by removing the primary sex glands, and since the normal female shows about twice the activity of the male (Hitchcock, 15) it would seem that the palm goes to the ovary.

CORRELATION OF VOLUNTARY ACTIVITY AND BASAL METABOLISM

Dr. Milton O. Lee, who has given special attention to this topic, has supplied me with the following notes. It might be supposed that there is a causal relationship between the basal metabolic level in an animal and the amount of voluntary activity which it shows. Data from a number of sources give some information on this point.

1. *The effect of thyroidectomy.* Removal of the thyroid glands, which are primary regulators of metabolism, has been shown to have no effect whatever upon the voluntary activity of rats. In a series of 20 experimental and 20 control animals the average daily activity was almost exactly the same in each group.

2. *The oestrous cycle.* If there exists any correlation be-

tween the general metabolic level and the amount of voluntary activity, one would expect to find an increased basal metabolic rate during those stages of the oestrous cycle characterized by increased activity. In stage II of the cycle, for example, the voluntary activity is increased 200 to 400 per cent over the level in the other stages. At this time, however, there is no signficant change in the basal metabolic rate. At least 50 determinations of basal metabolism during the oestrous stage in 10 different rats failed to show any constant increase or decrease as compared with the average level throughout the cycle.

Furthermore, there is an increase in the basal metabolic rate during the last few hours of the rest interval or Stage V of the cycle, when, however, there is no marked change in the voluntary activity. During the whole of Stage V of the cycle this activity is comparatively low.

3. *The effect of spaying.* Spaying has been shown to have a remarkable effect upon the voluntary activity, resulting in a decrease of 60 per cent or more. This decrease is not closely correlated with any decrease in the basal metabolic level. Determinations on five spayed rats over a period of three months have shown a decrease in basal metabolic rate of only about 10 per cent.

4. *Effect of ovarian hormone injection.* In two cases the basal metabolic rate was not changed upon the injection of ovarian hormone into spayed rats, even though rather typical oestrual cycles resulted.

In view of these facts, it seems possible to conclude definitely that there is no relation between the basal metabolic level and the amount of voluntary activity which the animal shows.

SUMMARY

In summary it may be said that determinations of spontaneous activity in rats kept in recording cages have disclosed no effects from thyroid or parathyroid extirpation or thyroid feeding. Adrenal extirpation often induces adynamia of from two weeks to permanent duration. Ergographic studies show reduction of work capacity of individual muscles to 1/16 normal. Glycerine extracts of adrenal gland (whole or cortex, only) by mouth or subcutaneously had no beneficial influence on voluntary

activity. Females are spontaneously more active than males, hence the ovarian hormone is presumably more potent than that of the testis. Castration and spaying results in marked decrease of spontaneous activity and of work capacity of individual muscles. Hysterectomy had no demonstrable influence. As shown by Wang activity can be restored approximately to normal by ovarian grafts. In our laboratory oral administration of glycerine extract of whole ovary, subcutaneous injection of saline extract of corpus luteum, saline prostatic extract and numerous sorts of testicular extracts, as well as testis feeding and vasectomy, have had no invigorating effect. Testis grafts have given almost but not quite completely negative results. No constant correlation between changes of basal metabolism and voluntary activity has been discovered.

BIBLIOGRAPHY

(1) Durrant: This Journal, 1925, **9**, 221-228.
(2) Durrant: Am. J. Physiol. (Balt.), 1924, **70**, 344-349.
(3) Gans & Miley: Am. J. Physiol. (Balt.), in Press.
(4) Wang: Comp. Psychol. Monogr. (Balt.), 1923, **2**, S. 6.
(5) Miley: Am. J. Physiol. (Balt.), in Press.
(6) Durrant: This Journal, 1926, **10**, 286-290.
(7) Durrant: Am. J. Physiol. (Balt.), in Press.
(8) Hoskins: Am. J. Physiol. (Balt.), 1925, **72**, 324-330.
(9) Gans: This Journal, 1927, **11**, 141-144 (this number).
(10) Gans: This Journal, 1927, **11**, 145-148 (this number).
(11) Gans & Hoskins: This Journal, 1926, **10**, 56-63.
(12) Hoskins: This Journal, 1925, **9**, 277-296.
(13) Smith: Am. J. Physiol. (Balt.), 1927, **80**, 114-126.
(14) Hitchcock: Am. J. Physiol. (Balt.), 1925, **75**, 205-209.

PSYCHIC TRAUMA IN PATHOGENESIS OF EXOPHTHALMIC GOITER*

A Review of 3343 Cases

ISRAEL BRAM, M.D.

From the Bram Goiter Institute, Upland, Penna.

PHILADELPHIA

The taking of a careful history in patients with exophthalmic goiter commonly yields three important facts: (1) Information to the effect that one or more blood relatives is or had been suffering with "nervousness," exophthalmic goiter, or diabetes mellitus; (2) the patient has been of more or less "nervous" temperament, characterized by irritability, impatience, fractiousness, and emotionalism, usually since childhood; (3) the onset of the symptoms of the disease followed soon after the occurrence of a psychic trauma.

From the frequency with which such histories are elicited, it appears that there is a strong congenital predisposition to the disease. Indeed, in quite a series of the cases herein reported, two, three, and even four members of a family have been afflicted with exophthalmic goiter. In the absence of an exciting cause, such a predisposition may not be recognizable nor tangibly mar the individual's physical and mental well-being throughout a normal span of existence. There are doubtless many thousands of individuals possessing a strong susceptibility to exophthalmic goiter who are going through life in an apparently normal manner, oblivious to possibilities which would likely follow the incidence of a psychic trauma.

The term psychic trauma applies itself to all conditions in which, with or without physical injury, the mind has received an impact or shock from which it does not readily recover to its former standard. The subconsciousness is especially involved. The shock may result from a cause acutely, subacutely, or chronically operative. The instinct of fear is the basis of

*Read before the Eleventh Annual Meeting of the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

psychic trauma and is unduly prominent in individuals susceptible to exophthalmic goiter.

PREDISPOSING "SOIL" IN TEMPERAMENT

As pointed out elsewhere,[1] we might state that the earmarks of susceptibility to exophthalmic goiter are: (a) heightened cerebration in which the mental alertness of the individual is above the average; (b) emotional instability; (c) excitable heart with labile pulse; (d) vasomotor ataxia characterized by dermographia, a tendency toward undue sweating, and undue surface heat; (e) sparkling eyes which during conversation and active attention may lead to a suspicion of exophthalmos; and (f) an unduly palpable thyroid gland which may, strictly speaking, still be within normal limits in size. These persons are to be found everywhere, more especially among Caucasians whose mentality is at the highest state of development. Psychologically, one might say that the chief characteristic of this class of individuals is an abnormally lowered threshold of emotional reaction.

EXCITING CAUSES OF EXOPHTHALMIC GOITER AS ELICITED IN 3343 PATIENTS OBSERVED IN 15 YEARS (JANUARY, 1911, TO JANUARY, 1926)

PSYCHIC TRAUMATA				General Infections (Influenza, Pneumonia, Syphilis, Etc.)	Focal Infections (in Teeth, Tonsils, Etc.)	Iodine Ingestion	Thyroid Extract Ingestion	No Stated Exciting Cause
Accident or Imminent Personal Danger (a)	Minor Surgery (Tonsillectomy, Curetage, Etc.) (b)	Parturition (c)	Worry, Grief, Disappointment, Sexual Incompatibility, Etc. (d)					
435	234	134	2039	100	67	100	33	201
(13%)	(7%)	(4%)	(61%)	(3%)	(2%)	(3%)	(1%)	(6%)

THE COMMON EXCITING CAUSE

The individual above described is singled out of the crowd to become the subject of exophthalmic goiter in a situation in which the instinct of self-preservation is called upon to decide between fight or flight. On the firing line in battle, during a conflagration, an earthquake, a shipwreck, or a train accident,

forty-nine out of fifty persons may emerge from the harrowing experience, quickly to recoil to usual physical and mental health. One of them, however, quickly or gradually develops symptoms merging into the typical picture of "frozen fright" characterizing exophthalmic goiter. The eyes stare, the heart palpitates, there is subjective and objective trembling, the skin is constantly moist, insomnia becomes complete, emotionalism dominates the mental existence, there is rapid loss in weight, and the basal metabolism rises beyond all bounds. This form of psychic trauma (accidents or imminent personal danger) was elicited in the histories of 435 patients, or 13 per cent. of this series. The following are typical examples:

1. Miss E. K., age 15, was in an automobile accident.
2. Mr. N. E., age 40, was struck by a trolley car.
3. Mrs. E. T., age 52, fell down a flight of stairs.
4. Mrs. M. P., age 26, was frightened by a fire next door. The following day the police raided her home by mistake.
5. Mrs. E. M., age 22, fell under a wagon.
6. Mr. E. K., age 32, while serving as government inspector in a munitions factory during the World War, saw a freight train jump the track and land into a warehouse filled with shells.
7. Mr. S. C., age 29, was made extremely nervous over the possibility of being sent to the front in the World War, though he had not yet been sent across the Atlantic.
8. Mr. J. O., age 32, drove his automobile in front of a train and made a very narrow escape.
9. Mrs. H. B., age 26, was very badly frightened by being informed that she was suffering with tuberculosis; shortly thereafter she participated in an automobile accident.
10. Mr. C. S., age 24, met with an accident in which he sustained the loss of an eye.
11. Mrs. E. G., age 31, was caught in a subway fire.
12. Dr. H. B., age 31, struck his head very forcibly against a steel beam.
13. Miss H. K., age 23, had a narrow escape from drowning.
14. Mr. S. A., age 32, had a narrow escape in a severe automobile accident.
15. Mr. L. B., age 32, was struck in the face by a golf ball.

Another form of acute psychic trauma may be described as resulting from the mental shock incident to surgical operations, usually minor, as tonsillectomy, nasal operations, uterine curetage, and the like. The number of patients presenting a history of the disease following minor surgery is 234, or 7 per cent. of the series. A patient may assume an air of bravado immediately before tonsils are removed, and yet become so badly frightened during the first few steps of the operation as to be shocked into the development of Graves' syndrome. This is no

argument against tonsillectomy in general. Since exophthalmic goiter following the shock of tonsillectomy almost invariably occurs in those operated upon under local anesthesia, it is suggested that the candidate for tonsillectomy be studied pre-operatively with a view to determining whether it would not be best to administer a general rather than a local anesthetic. The following are typical examples of this form of psychic trauma:

1. Mrs. A. O., age 24, had tonsillectomy performed two months before onset of symptoms.
2. Mrs. L. C., age 26, had tonsillectomy performed which was immediately followed by a "nervous breakdown" culminating in exophthalmic goiter.
3. Miss S. G., age 24, presents a similar history.
4. Mrs. M. S., age 26, stated that tonsillectomy was followed in three months by outspoken evidences of exophthalmic goiter.
5. Dr. E. R., age 42, presents a similar history.
6. Mr. M. M., age 28, had appendectomy performed. Patient states that it was not the operation but the ether that frightened him into the development of exophthalmic goiter.
7. Mrs. C. F., age 28, had a curetage without a general anesthetic.
8. Mr. R. MacD., age 43, stated that symptoms of exophthalmic goiter followed several days after the extraction of several molar teeth under local anesthesia.

Parturition, being associated with apprehension for self and offspring, as well as the ordeal of labor pains, is more likely to be the exciting cause of exophthalmic goiter than pregnancy itself, and constitutes an obvious psychic trauma. In this series, 134 patients (4 per cent.) developed exophthalmic goiter very shortly after delivery.

By far the greatest percentage of exciting causes was of a subacute nature, occurring under worry, grief, disappointment, and the like. Such a history was elicited from 2,039 patients, or 61 per cent. of this series. The following are typical examples:

1. Mrs. A. C., age 52, stated that her mother died of cancer. Immediately afterward she became obsessed with the thought that she, too, would die of cancer. Symptoms of exophthalmic goiter developed shortly after her mother's demise.
2. Mrs. E. L., age 53, claimed that symptoms developed as the result of financial worries and marital incompatibility.
3. Mrs. E. G., age 38, stated that the disease developed as a culmination of worriment over her daughter's unhappy marriage.
4. Mr. S. K., age 37, had severe financial strain during the past two years.
5. Mrs. E. K., age 48, had incessant worry over death of children.
6. Mr. S. G., age 30, experienced the shock of two deaths in the family.

7. Mr. H. H., age 37, had to carry a corpse down stairs; a few days later his brother died of influenza.
8. Mrs. J. K., age 20, was badly frightened when her baby fell off her bed.
9. Mrs. F. L., age 47, was "worried to death" over her child who had a double mastoid operation.
10. Mrs. H. S., age 48, received news of the sudden death of her mother and sister in Europe.
11. Mrs. I. S., age 24, suffered from shock because her child fell out of the second-story window and has since been suffering with convulsions.
12. Mrs. A. L., age 28, saw a horse run on pavement and jump over her child. Though the child was unhurt, the mother became hysterical and in a few days developed symptoms of exophthalmic goiter.
13. Miss R. B., age 25, witnessed the gasoline tank of an automobile and the occupant of the car on fire.
14. Mrs. S. G., age 30, saw her child develop convulsions.
15. Miss E. D., age 22, traced her illness to the time when her brother committed suicide.
16. Mr. S. B., age 41, stated that just prior to the onset of symptoms he had a nightmare in which a man with an axe was standing over his mother's bed and was about to decapitate her.
17. Mrs. A. B., age 43, saw her sister's baby burn to death.
18. Mrs. P. A., age 35, had a child who developed infantile paralysis.
19. Mrs. B. R., age 30, went to see a relative in an insane asylum, and on her way out of the institution her pathway was blocked by a lunatic.
20. Mrs. S. S., age 45, suffered from shock due to the death of both parents, which events were closely followed by a fatal accident to her brother-in-law.
21. Mrs. C. McA., age 38, was badly frightened by a negro breaking into her house to rob her.
22. Miss M. M., age 21, had a disappointment in a love affair.
23. Mrs. C. B. attributed her illness to the shock of the accidental poisoning of her child.
24. Mrs. B. T., age 25, was badly frightened by a man. She refused to give details.
25. Mrs. J. W., age 30, was suddenly awakened from sleep to be told that her next-door neighbor had died.

COMMENTS

Exophthalmic goiter appears to be increasing in all civilized countries. The high tension mode of existence during the past decade, with the multiplicity of automobiles, aircraft, highwaymen, "jazz" music, "jazz" thinking and acting, the craving to be entertained, the character of movie and stage presentations, marital incompatibilities and divorces,—all these and many more current factors activate to undermine the neuro-endocrine structures of susceptible individuals to the extent of increasing the incidence of the disease.

The time when the disease asserts itself following the occurrence of the psychic trauma varies with the intensity of the

trauma and the susceptibility of the individual. In quite a few instances of this series the symptoms of the disease presented themselves without any discernible interval of time between cause and effect. In most cases, however, several days or weeks elapsed before the patient became actively aware of the symptoms.

The degree of resistance manifested against the development of exophthalmic goiter may vary in the same person at different times. Also, an individual may be quite resistant to one form of psychic trauma, as, for instance, the shock of an automobile accident, yet become profoundly shocked by business reverses or by the sudden illness or death of a relative. The disease is instigated by an almost hair-spring mechanism and the zone of defense against exophthalmic goiter is so deficient in some individuals that a mere lover's quarrel may instigate the syndrome.

In approximately 15 per cent. of this series there occurred more than one psychic trauma to account for the syndrome. The first seemed merely to weaken the usual defense. Following the second or the third shock, the remaining resistance was broken down and exophthalmic goiter appeared in all its tragic picture.

In the female the psycho-sexual makeup plays a greater rôle in the pathogenesis of the disease than it does in the male. This is easily explained by the fact that the woman's life is largely dominated by her sexual existence, both from the standpoint of maternal instinct and from the fact that her sexual mechanism is much more complicated. Since sexual maladaptation is common, this form of psychic trauma is frequently encountered as the exciting cause of exophthalmic goiter.

Occupational, environmental and economical maladaptation and discontent are likewise forms of psychic trauma if continuous with no possibility of adjustment in view. This thwarting of happiness, apparently hopeless, may so prey on the mind of the individual as to constitute the exciting cause of the disease.

In probably 40 per cent of case histories the patient claims to have had a "nervous breakdown" weeks, months and occasionally a year or two preceding the onset of the existing syndrome. The "breakdown" is usually preceded by some emotional or nervous tension of acute or chronic nature, and is not followed by complete recovery. Some of the symptoms such as sensations

of trembling, apprehension, palpitation, restless sleep, and undernourishment still persist, although the individual as a rule is capable of resuming some or all of the customary duties. A relapse of the "breakdown" soon follows, which culminates in the syndrome of exophthalmic goiter.

While the patient is progressing toward recovery and still requires observation and the symptomatology is on the wane but has not yet disappeared, the resisting forces are as yet incapable of defending the individual against relapse. The patient is unsafe in an automobile accident, shipwreck or conflagration, or even in a family quarrel. An added shock in an improved patient may result in a symptomatology far more severe than that presented by the primary attack of exophthalmic goiter. It is only when the patient has been discharged cured and has been perfectly normal for about twelve months, that sufficient inhibition to combat the marked effects of psychic traumata is exhibited.

INFECTIONS IN ETIOLOGY OF EXOPHTHALMIC GOITER

Such general infections as influenza, pneumonia, tuberculosis, and syphilis constitute the exciting cause in one hundred of our series of cases, or about 3 per cent. It would seem that a general infection is coincidental, rather than causal. Possibly the more common cause of exophthalmic goiter, though not elicited, was present but unrevealed by the patient.

The same might be said of focal infections in teeth, tonsils, sinuses, Fallopian tubes, and elsewhere, which in this series presented 67 instances or 2 per cent of the total. Though on general sound principles we must remove diseased tonsils in all goiter patients, these and other infectious foci probably play but a contributory etiological rôle in exophthalmic goiter. Tonsillectomy with the expectation of curing exophthalmic goiter is usually disappointing; this procedure should be regarded as merely supplementary to more direct therapeutic measures in the management of the disease. Bearing in mind the possibility of aggravating the symptoms of the disease by added shock, the time when tonsillectomy should be performed and the nature of anesthetic to be employed should receive due consideration.

IODINE INGESTION IN ETIOLOGY

The publicity to further the use of iodine through the ingestion of this drug in drinking water, iodized salt and in innumerable other forms, with a view to the prevention of goiter, has resulted in so many instances of harm that the medical profession is awakening to the importance of raising a protest against unguided and indiscriminate administration of this substance. Through its tendency to increase the colloid content of the thyroid gland, iodine very frequently increases the size of simple and of hyperplastic goiter of Graves' disease to an alarming degree. Through its tendency toward whipping up the function of the thyroid, iodine is capable of converting a simple adenoma into a toxic one, and a toxic hyperplastic thyroid into one whose hyperfunction knows no bounds and endangers the life of the individual. While the majority probably are capable of withstanding iodine ingestion, a percentage of individuals susceptible to exophthalmic goiter react in a manner almost corresponding to the infliction of psychic trauma. One hundred patients of our series (over 3 per cent) presented a history in which no exciting cause was discoverable other than the ingestion of iodine for the cure of an imaginary or actual slightly swollen thyroid. The discovery of the existence of an unduly palpable thyroid gland leads to a kind of goiter phobia, and then follows the ingestion of iodine either through the busy medical attendant, or through self-administration induced by popular literature and advertisements.

INGESTION OF THYROID EXTRACT IN ETIOLOGY

What has been stated respecting iodine may be doubly emphasized regarding thyroid extract. The unfortunate tendency of today in the direction of becoming and remaining thin to keep pace with the dictates of dame fashion has resulted in an avalanche of obesity "cures" described in newspapers and magazines. Nearly all contain thyroid extract, iodine, or both. Those containing thyroid extract must of necessity possess its iodine content. Thirty-three patients, or one per cent of our series presented a history of the ingestion of thyroid extract as the only explicable reason for the development of the disease.

One might rightly ask: If thyroid extract is more capable

of producing exophthalmic goiter than is iodine, why so comparatively few cases of the disease from ingestion of thyroid extract? The answer is to be had in the tremendously increased publicity given the use of iodine and iodine-containing nostrums as compared to the publicity given thyroid extract and obesity "cures." Moreover, the effect of thyroid extract ingestion is more prompt and startling. The average patient feeling sick after the taking of a few tablets of thyroid extract becomes alarmed, discontinues it, and may recoil back to the former sense of well-being. Not so with iodine, which may be taken for many months without a realization of resultant harm.

The question again arises: Since thyroid extract ingestion is said by many investigators to be capable only of producing hyperthyroidism in man, how does it produce exophthalmic goiter? The answer lies in the type of individual taking it. In other words, it is *susceptibility* to exophthalmic goiter that is as much the determining factor as thyroid extract.

EXOPHTHALMIC GOITER WITHOUT DISCOVERABLE EXCITING CAUSE

Despite careful history-taking and physical examination, 201 patients (6 per cent of this series), presented no exciting cause to account for the onset of exophthalmic goiter. It is felt that in most of these there existed one or other of the aforementioned exciting causes, probably psychic trauma, but unrevealed by the patient. Though it would seem that a psychic trauma resulting in the development of exophthalmic goiter would make an indelible impression upon the patient's mind, this is frequently not the case, especially when bodily injury was not sustained. In many patients in whom there was an unmistakable history of psychic trauma, this information was obtained only after the second or third interview, or occasionally through an almost psychoanalytical process. It was then that the event suddenly loomed forth in the patient's mind in all its detail, and the history was completed. It is therefore evident that in hasty history taking this valuable information may be lost. Our histories require more than an hour of questioning, and half the time thus expended is devoted to an inquiry into the mental life of the individual. Despite extreme care, it is felt that occasionally a patient has undergone a psychic trauma, the nature of which is distasteful to narrate, hence remains for-

ever unrevealed to the physician. Moreover, we must not overlook the fact that many patients applying for treatment realize the mistake in having taken iodine or thyroid extract prior to the onset of the illness and do not care to discuss this matter. Were we able more keenly to scan the inner life and past experiences of these patients it is very likely that the instances yielding no history of exciting cause would be reduced to zero.

CONCLUSIONS

1. In this series of 3343 cases of exophthalmic goiter, 2842 or 85 per cent presented a clear history of psychic trauma as the exciting cause of the disease. In 167 cases or 5 per cent of the series, there was elicited a history of general or focal infection as the probable exciting cause of the disease. In 133 cases or 4 per cent of the total the ingestion of iodine or of thyroid extract in tablets or in the form of obesity "cures" was regarded by the patients as the cause of the symptoms. In 201 cases or 6 per cent, there was no discoverable exciting cause to account for the onset of the disease.

2. It is felt that in most instances in which infections appear to serve as the exciting cause and in those in which no exciting cause was discovered an unrevealed psychic trauma may have been the exciting cause to account for the onset of the disease.

3. Since psychic trauma appears to be the exciting cause in the vast majority of cases of exophthalmic goiter, it would appear that this factor more closely approaches the solution of the question of its etiology than any other theory.

4. The predisposition or "soil" upon which the exciting cause is superimposed is usually an inherited and occasionally an acquired peculiarity of the individual.

5. These data point strongly to the irrationality of thyroidectomy in the treatment of exophthalmic goiter. Therapeutic approach, to be fundamentally successful, must be broad and seek to establish the proper equilibrium of the involuntary

mechanism of the body through measures directed toward endocrine and mental adjustment. Moreover, recovery must be made conclusive by efforts at increasing the zone of defense against the tendency toward relapse.

BIBLIOGRAPHY

1. Bram, I.: Prevention of exophthalmic goiter, This Journal, 1923, **7**, 415-430.

STUDIES OF THE THYROID APPARATUS. XLVIII
AGE, SEX, WEIGHT, AND SEASON AS LETHAL FACTORS IN CONDITIONS OF PARATHYROID AND THYROID DEFICIENCY

FREDERICK S. HAMMETT

The Wistar Institute of Anatomy and Biology

PHILADELPHIA

A study of the role of the thyroid apparatus in growth and development would be incomplete were there to be omitted an analysis and brief report of the indications obtained with regard to age, sex, weight, and season differences in mortality subsequent to the glandular removals.

Although the number of animals available for this phase of the work is large, the multiplicity of classes into which they are distributed, as seen from table 1, makes conventional statistical analysis impossible. Nevertheless, proper and legitimate arrangements of the data bring out significant differences from which justifiable conclusions may be drawn.

Before setting down the main thesis of the paper, note should be made of certain differences in reaction to the two types of glandular deficiency. From table 2 it is seen that the per cent

TABLE 1

THE DISTRIBUTION OF THE RATS USED IN THIS STUDY ACCORDING TO AGE, SEX, AND TYPE OF GLANDULAR DEFICIENCY

Age in Days	*Thyro-parathyroidectomized*			*Parathyroidectomized*			*Totals on Age*
	Males	*Females*	*Totals*	*Males*	*Females*	*Totals*	
14.....	13	29	42	9	16	25	67
23.....	134	97	231	86	27	113	344
30.....	78	90	168	36	39	75	243
50.....	47	62	109	35	47	82	191
65.....	31	29	60	40	34	74	134
75.....	52	39	91	39	34	73	164
100.....	21	27	48	21	20	41	89
Totals.	376	373	749	266	217	483	1232

mortality is pretty generally less in the parathyroidectomized than in the thyro-parathyroidectomized groups.

TABLE 2

THE PER CENT MORTALITY ACCORDING TO AGE, SEX, AND GLANDULAR DEFICIENCY

Age in Days	—14—		—23—		—30—		—50—		—65—		—75—		—100—	
	TP	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*
Male	85	78	83	75	83	50	53	52	48	60	56	49	19	14
Female	72	75	73	33	70	64	71	60	48	44	64	50	47	5

TP—Thyro-parathyroidectomized. PT—Parathyroidectomized.

This would seem to indicate that the parathyroid deficiency produces a less harmful effect than does thyro-parathyroid. Consistent with the foregoing is the fact that a like direction of difference occured in the growth reactions of the two groups. The details are given in preceding papers. This supports the idea that a difference in the degree of nutritional defect is a factor in the production of the difference in mortality rate, as well as in the production of the differences in growth rate. The similarity is further enhanced by the fact that the sex-specific increase in growth sensitivity of the parathyroidless males at puberty (65 days of age), is mirrored by a relative increase in the per cent mortality at this time. On the other hand, as will be shown, initial body weight is undoubtedly a factor conditioning survival (Table 4). Hence, since the body weight of the parathyroidectomized rats at the time of operation was more, on the average, than that of the thyro-parathyroidectomized, and since the greater number of deaths in both groups occurred shortly after operation because of acute parathyroid deficiency it is probable that the chief factor in the lesser mortality rate of the parathyroidectomized groups is rather the greater initial body weight with all that this implies, than the lesser degree of nutritional defect subsequently induced.

With this preliminary differentiation, we can now go on to the other factors. The two types of glandular deficiency will be considered as a single lethal factor. First, because age, sex, weight, and season are inherently conditioners of the general biological substratum, and, second, because the immediate cause of death in the majority of cases is acute parathyroid deficiency.

The Age as a Factor. The per cent mortality of the rats on age is given in Table 2. Now 150 days of age was taken as the end of the period of observation of growth. Hence, the

minimal standard interval between glandular removal and autopsy was 50 days. Therefore those few rats which lived more than 50 days, but died before they were 150 days old, are omitted from the computations.

From the table it is clear that in general a decrease in mortality rate accompanies the increase in age at time of the initiation of the glandular deficiency. Young rats are more liable to death than old ones.

Suggestions of a like difference in dogs were reported by Rosenblatt in 1894 (1), and in sheep by Simpson in 1913 (2). This age difference in sensitivity is correlatable with the occurrence of idiopathic tetany in man. While the origin of this disorder is obscure, it is possible that parathyroid deficiency is a factor (3).

The distribution of my material is such that seasonal influence is discountable in this age tabulation. The difference is a real expression of the influence of age. The occurrence of the relation in several species marks the phenomenon as one of fundamental biological significance. Particularly is this true since it contravenes in direction the usual age difference in sensitivity to poisons (4).

The explanation is elusive.

Some years ago I showed that rats in which instinctive reactions productive of tenseness or heightened muscle tone had been minimized by gentling, were much less liable to death in *tetania parathyreopriva,* than rats in which these emotional attitudes were given their usual play (5, 6). We have here a potentially similar situation. For although all the rats used in these growth studies were gentled from birth on, it is obvious that the younger animals were subjected to this process for a shorter period before the glandular removals. Combining this with the fact that young animals are naturally more excitable, it is obvious that in this series we may well have had a roughly graded decrement in tonal status with increasing age. The two sets of data are thus seen to be consistent.

Such being the case, and until more explicitly definitive data with regard to the causative mechanism of parathyroid tetany are available, a tentative explanation of the age difference in mortality rate can be based on the same general principles as

that given for the difference in mortality rate of the gentled and wild rats.

It is assumed that the tetany which leads to death in conditions of parathyroid deficiency is in part due to a non-disposal of some toxic product arising from muscle-tonus metabolism. If this is so, it would be expected that the younger animals of greater relative productivity of this hypothetical substance, because of greater excitability and consequently greater muscle tonus, would succumb in greater numbers on loss of the protective function afforded by the parathyroids, than would the older rats of lesser activity.

Although fact coincides with theory on both counts, the interpretation is more suggestive than adequate. In any final analysis, the relationship between parathyroid function and calcium exchange, and calcium and neural irritability cannot be neglected (7).

The values in Table 2 give a hint that the onset of puberty is a factor in the shift from the high to the low mortality rate. This is not inconsistent with the foregoing interpretation.

The average corrected length of survival period after the glandular removals at the several ages is given in Table 3. The few values obviously beyond the usual range were omitted from the computations. The table shows that the young rats survived the deficiency longer than the old. This is probably due to the higher rate of metabolism in the young, which presumably would facilitate the disposal of toxic products. The delay is therefore consistent with the interpretation of the age difference in per cent mortality. It is also consistent with the usual age difference in reaction to poisons in general (4).

The Sex as a Factor. From Table 2 it is seen that there is no consistent sex difference in per cent mortality on age. From Table 3 the suggestion is had that the males tend to survive the loss of the thyroid and parathyroids a bit longer than do the females. In general, however, sex differences in mortality are

TABLE 3

AVERAGE CORRECTED SURVIVAL TIME AFTER THYRO-PARATHYROIDECTOMY AND PARATHYROIDECTOMY AT THE DIFFERENT AGES

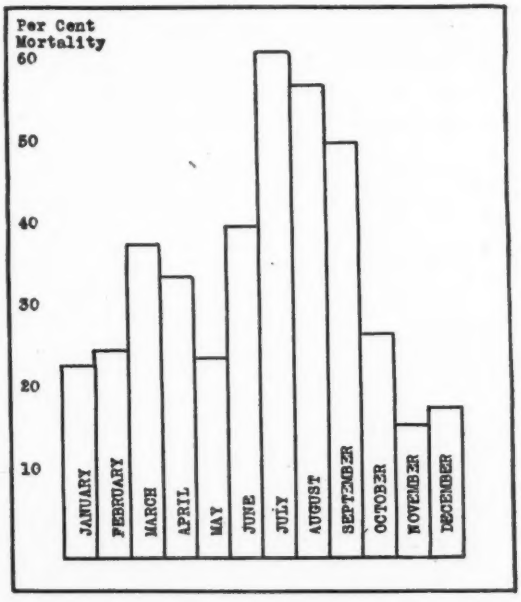
Age in Days	—14—		—23—		—30—		—50—		—65—		—75—		—100—	
	TP	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*	*TP*	*PT*
Male	11	20	7	12	7	7	6	2	4	3	4	6	20	2
Female	11	21	8	9	5	5	3	2	3	3	6	4	5	1

TP—Thyro-parathyroidectomized. PT—Parathyroidectomized.

not demonstrable. Hence sex can hardly be considered as a lethal factor in conditions of parathyroid deficiency.

The Initial Body Weight as a Factor. In Table 4 the average initial body weight of the rats which died during the first three days after operation is compared with that of those which lived until 150 days of age. The three-day interval is taken as the standard, because it is during this period that the large majority of the animals die from the acute effects of the glandular deficiency. No rats dying from the effects of the operative technic were included in the compilation. Only those rats the death of which was due to parathyroid toxemia were used.

Chart 1



The month by month per cent mortality of the rats dying from parathyroid deficiency within three days of the glandular removal.

It is evident that the average initial body weight of the survivors was greater than that of those which died. If body weight is taken as a mark of the general nutritional condition, and such is permissible when groups of rats of like age and source are

compared, it is clear that a sub-average nutritional status is a lethal factor in conditions of parathyroid deficiency.

The Season as a Factor. On Chart I is shown the month by month per cent mortality of the rats dying within three days of the glandular removal.

TABLE 4

AVERAGE INITIAL BODY WEIGHT OF RATS THAT DIED WITHIN THREE DAYS AND OF THOSE THAT LIVED TO 150 DAYS

	Thyro-parathyroidectomized				*Parathyroidectomized*			
	—Male—		*–Female–*		*—Male—*		*–Female–*	
	Died	*Lived*	*Died*	*Lived*	*Died*	*Lived*	*Died*	*Lived*
	gm.	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*
14.....	14	18	15	19	..	17*	..	20*
23.....	27	29	27	27	27	26	31	30
30.....	43	40	38	39	34	43	33	39
50.....	69	77	74	75	63	74	73	77
65.....	105	119	102	102	104	123	88	104
75.....	118	135	105	113	127	140	96	114
100.....	120	163	127	136	136	160	140	134
Averages	71	83	70	73	82	94	77	83

* Omitted from the averages.

It is evident, from the increased mortality rate, that a decrease in resistance to parathyroid deficiency occurs during the spring months of March and April. This finding is quite the same as that of Cameron and Carmichael (8), who observed that their rats were increasingly subject to tetanic seizures during these months. Furthermore, this increase in sensitivity coincides with the seasonal increase in incidence of idiopathic tetany in man as recorded by Barker (3). The syndromal and seasonal similarity suggest that the latter disorder is associatable with parathyroid deficiency. This idea is further strengthened by the fact recorded in an earlier paragraph, that the age of lesser resistance to parathyroid deficiency in the rats, as evidenced by the high mortality rate, roughly coincides with the age of greater incidence of idiopathic tetany in man. The general correlation is probably more than fortuitous.

Cameron and Carmichael (8) imply in their paper that a fall in barometric pressure accompanied by a sudden marked

rise in atmospheric humidity is a probable cause of tetanic seizures. Unfortunately I am unable to give any data on the atmospheric pressure in relation to the mortality rate in my series. From the chart, however, it is clear that the per cent mortality is markedly increased just during those months when the Philadelphia climate is exhibiting its characteristic exacerbations of humidity and heat. The spread of this combination is rather broader here than in Canada. So the correlation between the two, in my series, is substantial confirmation of Cameron and Carmichael's postulate. The fact that these data are based on records gathered over a period of five years is further support for the interpretation.

These seasonal peaks in mortality are roughly similar in time of occurrence to those observed by Pritchett (9) on the reaction of mice to inoculation with paratyphoid bacillus, and to those observed by Pearce, Brown and Van Allen (10) with regard to the malignancy of implanted tumor tissue. Such being the case, it is assumable that the sensitivity of the animal organism at these times is not specific but general. That is to say, the resistance capacity is lowered, so that any potentially harmful influence is more productive of disturbance than at other times, other things being equal. Whether or not this principle can be extended to man is a matter which can only be solved by a carefully controlled statistical analysis, in which account is taken of regional differences in climate.

CONCLUSIONS

Age and season are factors influencing the sensitivity of the albino rat to parathyroid deficiency. There is good correlation between the reaction to these influences and the incidence of idiopathic tetany in man. This suggests that the latter disorder is associated with a disturbance of parathyroid function.

Since the seasonal increases in sensitivity are not confined solely to reaction to parathyroid deficiency, but are exhibited to a variety of noxious stimuli, it is probable that they represent periods of decreased resistance to any potentially harmful influence.

Initial body weight is also a factor conditioning the mor-

tality rate after parathyroid removal. The per cent mortality is higher in the groups of lower average body weight.

No evidence is available that sex is a factor.

BIBLIOGRAPHY

1. Rosenblatt, J.: Arch. Soc. Biol., St. Petersb., 1894, **3**, 53.
2. Simpson, S.: Quart. J. Exp. Physiol., 1913, **6**, 119.
3. Barker, L.: Endocrinology and Metabolism. 1922. Appleton, N. Y. and London. Vol. 1.
4. Hammett, F. S., & Nowrey, J. E., Jr.: J. Pharm. & Exper. Therap., 1922, xix, 331.
5. Hammett, F. S.: Am. J. Physiol., 1921, **56**, 196.
6. Hammett, F. S.: This Journal, 1922, **6**, 221.
7. Hammett, F. S.: Am. J. Physiol., 1927, in Press.
8. Cameron, A. T., & Carmichael, J.: Trans. Roy. Soc., Canada, 1926, 3rd Ser., **20**, Sect. V, 277.
9. Pritchett, I. W.: J. Exp. Med., 1925, **41**, 209; 1926, **43**, 173.
10. Pearce, L., Brown, W. H., & Van Allen, C. M.: J. Exp. Med., 1924, **40**, 603.

THE ACTION OF ULTRA-VIOLET LIGHT, THYROID AND PARATHYROID SUBSTANCES UPON AN ARTIFICIAL PLASMA IN VITRO

H. W. C. VINES, M.D.

From the Pathological Laboratory

CAMBRIDGE, ENGLAND

This investigation is an attempt to define more clearly the actions which ultra-violet light, thyroid and parathyroid gland substances exert upon the calcium content of the plasma in the body, with special reference to the changes which occur in rickets. The prevalent views of the actions of these agents seem to be that the parathyroid glands are responsible for the retention of calcium and the thyroid in part for the loss of calcium from the body. There does not appear to be any very clear definition of the action of ultra-violet light beyond the fact that it is of undoubted value in raising a lowered plasma calcium and in stabilizing calcium metabolism in certain conditions such as rickets. Grant and Gates (1) have shown that hypertrophy of the parathyroid glands occurs in animals which are exposed frequently to ultra-violet light, and it is known that a seasonal hypertrophy occurs in summer. Beyond these points there does not seem to be any very clear relationship between ultra-violet light and the glandular regulating mechanism of calcium metabolism.

The method of investigation was to study the variation in the calcium content of a special solution in the presence of an excess of solid calcium phosphate, before and after exposure to ultra-violet light and the introduction of thyroid and parathyroid gland substance. The conditions of experiment were as follows:

THE SOLVENT

The basis of the solution used was an aqueous saline solution containing 0.6% NaCl, 0.2% $NaHCO_3$, and 0.1% glucose. To this were added certain organic substances to represent the corresponding groups in the plasma. Dried egg-white was used to represent the plasma proteins, and there were also added

lecithin, pure cholesterol and cholesteryl oleate, the latter to represent the cholesteryl esters of the plasma. Since it was found difficult to work with a solution containing 7 gms. of protein per 100 cc., which is approximately the concentration in the plasma, solutions containing 2% and 3% protein were used. In these the ratio of lecithin and cholesterin fats to the protein concentration was made the same as that found in the plasma. Carbon dioxide was then passed through the solution until pH 7.4 was reached, as determined colorimetrically with phenol red. The solid dibasic phosphate of calcium was then added in increasing amounts, starting with the addition of 12.5 mgm. per 100 cc. of solvent, and increasing by 12.5 mgm. at a time until 200 mgm. were reached. Actually 400 cc. of the solution was used at a time, so that in each experiment a series of flasks were necessary, the first containing 50 mgm. of the added phosphate, the next 100 mgm., the next 150 mgm. and so on. This mixture was incubated at 37°C for forty-eight hours, after the addition of a little chloroform. The hydrogen-ion concentration was then estimated colorimetrically, the solution filtered rapidly and the calcium and phosphorus contents of the clear filtrate were determined after removal of the protein by boiling with an acetic acid and sodium acetate mixture. The calcium was determined gravimetrically as the oxalate and the phosphorus by titration against a standard uranium solution.

It may be objected that the incubation period of forty-eight hours is insufficient to allow of the establishment of a true equilibrium between the solid and dissolved phases of the calcium phosphate, since it has been repeatedly shown that, using a simple saline solution, weeks or even months are necessary for true equilibrium to be obtained. In the present experiments, however, the solvent is not a simple saline solution. Further, there is no evidence to show that after the plasma calcium has been reduced, these long periods of time are required until the normal value is regained. In normal dogs the blood calcium may be rapidly and largely increased by the injection of Collip's parathyroid extract alone, and there is reason to believe that the additional calcium is mobilized from the skeleton. Again, after the blood calcium has been reduced as in the tetany of rickets or after parathyroidectomy to values below those ob-

tained in the present experiments, it may be increased by the use of parathyroid extract or ultra-violet light to a degree and with a rapidity sufficient to abort an imminent attack of tetany. It must be admitted that the adjustment in the body between the dissolved and solid phases of the calcium phosphates is a rapid one and does not require an indefinitely long period of time for its accomplishment. Whether this adjustment represents a complete or a partial equilibrium, is a matter with which the present investigation is not concerned.

In regard to the present experiments, it is evident that a uniform equilibrium has not been obtained in every flask, as may be seen from the calcium values in any of the charts. But in all cases the variation of the points justifies the average curve which has been drawn, and indicates that in each chart an approximate equilibrium has been obtained in the time period used. Since in all cases the medium and all other conditions of experiment were as nearly as possible constant, the curves are reasonably comparable and sufficiently so to determine whether the agents investigated have had any effect upon the medium.

At the two protein concentrations used, the composition per 100 cc. of the solvent was as follows:

	I.	II.
NaCl	0.6 gms.	0.6 gms.
$NaHCO_3$	0.2 gms.	0.2 gms.
Anhydrous glucose	0.1 gms.	0.1 gms.
Dry egg-white	2.0 gms.	3.0 gms.
Lecithin	0.06 gms.	0.09 gms.
Pure cholesterol	0.011 gms.	0.018 gms.
Cholesteryl oleate	0.014 gms.	0.021 gms.
Initial pH	7.4	7.4

THE AGENTS INVESTIGATED

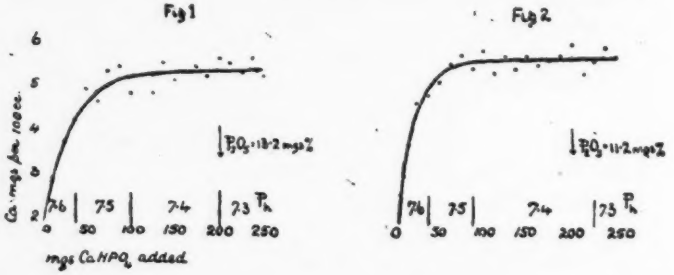
a. *Ultra-violet light.*

Exposure to ultra-violet light was in all cases carried out as follows: Four hundred cc. of the solution were exposed in a quartz flask to the light of a quartz mercury-vapour lamp for fifteen minutes at room temperature with constant shaking. The

distance from the arc was three feet. Irradiation was carried out before the addition of the calcium phosphate and at pH 7.4.

b. *The gland substances.*

Parathyroid and thyroid substances were used in the form of the fresh gland, dried powders and also thyroxin. To each 100 cc. of the solution 8 mgs. of the dry gland or 40 mgs. of the fresh material were added. In the present paper only the results obtained with the fresh gland substance will be considered. Experiments were carried out before and after exposure to ultraviolet light. In certain cases one or more constituents of the solvent were left out in order to determine the one through



which the gland substance exerted its action; these cases will be referred to individually.

THE RESULTS OBTAINED

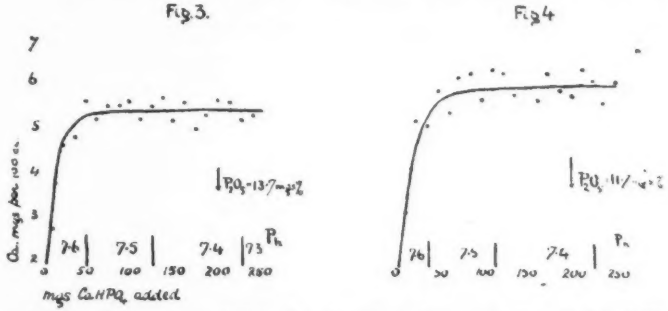
In the accompanying figures the calcium concentrations in the solvent are plotted against the amount of solid calcium phosphate added to the solution. The variation in the reaction of the medium is also shown, and the phosphorus concentration is given in all cases at a value of 200 mgm. of added phosphate. The calcium values actually obtained are shown as points, the curve representing an approximate mean.

Figs. 1 and 2 show the degree of equilibrium attained when the solvent as described was in contact with solid calcium phosphate for the stated time without the addition of any of the agents under investigation. Fig. 1 represents Solution I in the table previously given, and Fig. 2 Solution II. The differences in the two figures are but slight and can be accounted for by

the presence of an additional one per cent of protein in the second solution. These two figures serve as the basis for comparison with the results obtained when the agents under investigation are present.

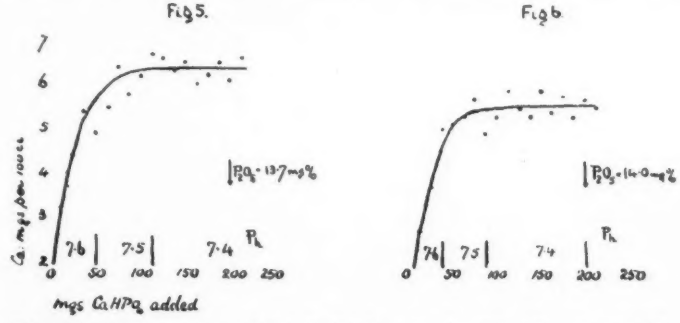
a. *Ultra-violet light.*

The effect of exposure to ultra-violet light is shown in Figs. 3 and 4, comparable with Figs. 1 and 2. The changes induced are only very slight. There is a slight increase in the



calcium content, no change in the phosphorus and a slight shifting of the reaction of the medium to the alkaline side.

The free cholesterol of the medium was then replaced by its equivalent of cholesteryl oleate. The result of exposure of

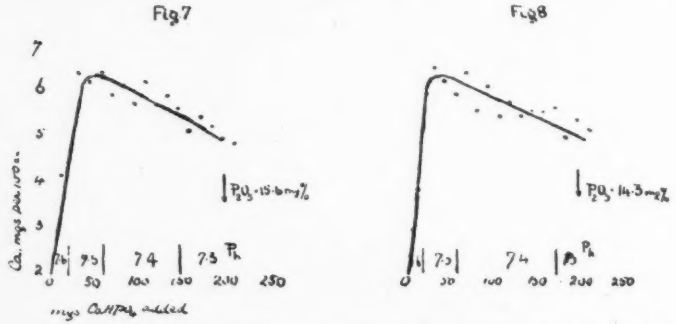


this solution to ultra-violet light is seen in Fig. 5, comparable with Figs. 1 and 3. There is now a definite increase in the calcium content and a shifting of the reaction of the medium to the alkaline side, while the phosphorus content remains un-

changed. On omitting the cholesterol fats altogether (Fig. 6) these changes disappear and a picture very similar to Fig. 1 is obtained; this result was also obtained when the cholesteryl oleate was left out and the pure cholesterol retained in the solution. This would suggest that the action of ultra-violet light is produced through the cholesteryl esters rather than the free cholesterol.

b. *Parathyroid gland.*

The substance next investigated was fresh parathyroid gland (Figs. 7-11). Figs. 7 and 8 were obtained after the addition of the gland substance in the amount already given and without exposure of the solution to ultra-violet light; they are com-

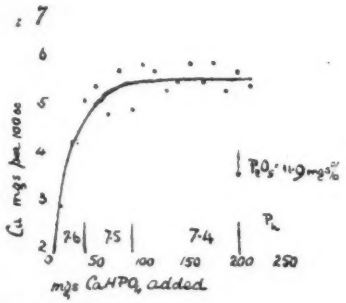


parable with Figs. 1 and 2. There is a definite change in the calcium and phosphorus contents of the solution; the latter is increased and there is a shifting of the reaction of the medium to the acid side. The maximal value of the calcium content of the solution is increased, but it is evident that this happens only on the alkaline side of pH 7.4, for as the acidity of the solution increases its calcium content falls rapidly. In Fig. 9 the experimental conditions were the same as in Fig. 8, except that the cholesterol fats were omitted from the solution. The picture obtained is almost identical with Fig. 2, suggesting that the parathyroid gland produces its effect also through the cholesterol fats.

Figs. 10 and 11 show the effect of the combined action of parathyroid gland and ultra-violet light (cf. Figs. 3 and 4). It is seen that the changes described in the last paragraph have

disappeared. There is a slight but constant increase in the calcium value, the curves are of the usual type, the phosphorus content is reduced, while the range of variation in the reaction of the medium has become similar to that in the two first figures. This would suggest that the ultra-violet light has had a neutralizing effect.

Fig 9.



c. *Thyroid gland.*

On comparison with Figs. 1 and 2, Figs. 12 and 13 show a definite increase in the calcium contents, while the phosphorus remains practically unchanged. There is, however, a considerable shifting of the reaction of the medium towards the acid

Fig 10.

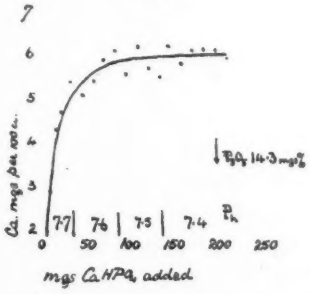
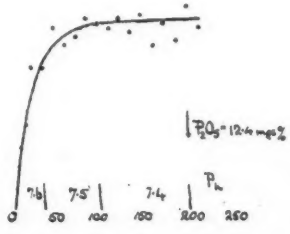


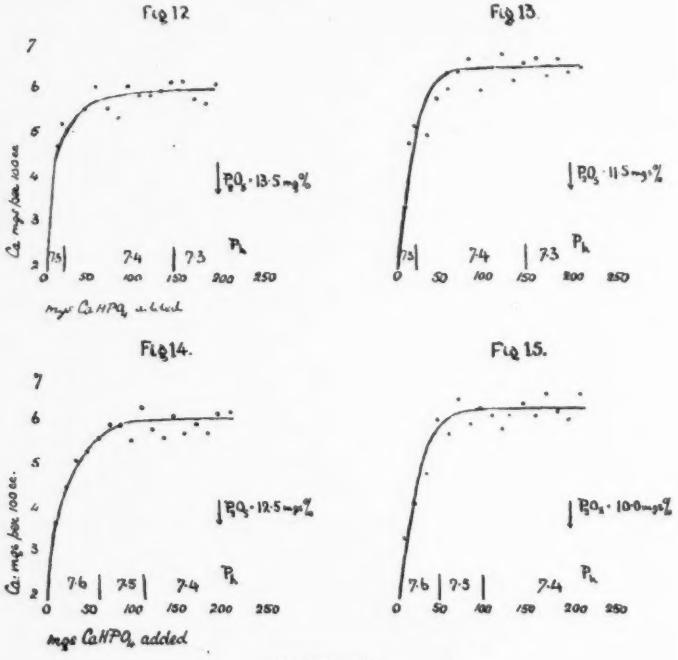
Fig 11



side. After omitting the cholesterol fats from the solution these changes were still present.

After exposure to ultra-violet light (Figs. 14 and 15) the increase in calcium is to some extent maintained. But the alka-

linity of the solution has now been considerably increased and the phosphorus content is lower than in the corresponding Figs. 3 and 4. Again it is evident that the effect of exposure to ultra-violet light is towards stabilizing the reaction of the medium.



DISCUSSION

So far as these experiments go, the general conclusions which may be drawn are as follows: parathyroid gland substance increases the calcium content on the alkaline side of pH 7.4, but causes a rapid decrease as the acidity of the solution rises; thyroid substance increases the calcium content of the solution on the acid side, while ultra-violet light in either case has a stabilizing action such that the increases of the calcium contents effected by the gland substances are maintained as maximal about pH 7.4. The effect of the light is shown chiefly by the reduction of the phosphorus contents of the solution, perhaps by some combination between a calcium cholesteryl ester and the

phosphoric ions. This neutralizing effect is seen in each of the three sets of experiments, and it suggests the possibility that ultra-violet light may play some part of importance in the maintenance of the neutrality of the tissues. It is of interest to recall that in nephritic and diabetic acidosis there is a marked disturbance of cholesterol metabolism resulting in a great increase of the cholesterol fats. In nephritic acidosis, in which there is a considerable retention of acid phosphates, the increase in cholesterol fats is due largely to the increase in cholesteryl esters (2). It is of further interest to note that Bergstrand (3) has recorded a small number of cases of nephritis in which parathyroid hyperplasia was present.

The question of parathyroid hyperplasia in conditions which may involve skeletal decalcification is of considerable interest. Pappenheimer and Minor (4) record fourteen cases of rickets with parathyroid hyperplasia, Ritter (5) ten cases and Hartwich (6) twenty-three cases. Erdheim drew attention to the condition in rats rendered rachitic experimentally, while Luce (7) observed it in rats undergoing calcium starvation. Ghiron (8) refers to some thirty cases in the literature of parathyroid hyperplasia in osteomalacia, while Falta (9) considers that parathyroid hyperplasia almost always accompanies this condition. In view of the rarity with which systematic examination of the parathyroids is carried out at autopsies, the association of parathyroid hyperplasia with skeletal decalcification would seem to be an intimate one.

That this hyperplasia is not a defensive attempt to cause increased ossification is indicated by the fact that Korenchevsky (10) failed to find that parathyroidectomy hastened the onset of rickets, and further there is no evidence that true rickets has ever followed simple parathyroid removal. But since there is a continual and excessive loss of calcium from the body, it may be possible that the parathyroid hyperplasia is an attempt to maintain, not the calcium content of the skeleton, but that of the body fluids at the expense of such ossified tissue as there may be. There is no evidence that parathyroid therapy alone will permanently benefit rickets or osteomalacia, just as ultra-violet light fails to benefit permanently the calcium deficiency of parathyroidectomy or of parathyroid tetany. Collip (11) has

indeed succeeded in aborting the onset of rachitic tetany by the use of his parathyroid extract, just as Turpin (12) aborted but failed to cure the tetany in a case of tetania parathyreopriva. The effect, in the former case, at least, may be due to an acceleration of the skeletal decalcification which raises the blood calcium temporarily above that value below which tetany is liable to occur.

Since in rickets there is a greater or lesser deficiency of the ultra-violet factor, the results shown in Figs. 8 and 13 become pertinent to the discussion, on the assumption which is supported both clinically and experimentally, that the thyroid and the parathyroid glands are largely concerned in the regulation of calcium metabolism. In the absence of ultra-violet light (Fig. 13) the thyroid increases the acidity of the solution while the calcium remains fairly constant. But in Fig. 8 it is seen that at the degree of acidity shown in Fig. 13 the parathyroid is not maintaining the calcium level, but is causing a fall of a degree considerably greater than the increase effected by the thyroid in Fig. 13. In rickets the deficiency of the light factor leaves these two glands largely responsible for the regulation of calcium metabolism, and it has been shown clinically that not only may parathyroid hyperplasia occur, but that a slight degree of acidosis is not uncommon. The experimental results suggest that the parathyroid glands will maintain an effective calcium concentration only on the alkaline side of pH 7.4 in the absence of ultra-violet light, and it seems possible that this may have some bearing on the decalcification of rickets.

A second parallel between these experiments and the conditions in rickets is seen in the effects of ultra-violet light in the two cases. Ultra-violet light produces permanent benefit in rickets. In the experimental solutions it causes a neutralization of the acidity in the case of the thyroid, and it inhibits the calcium loss from the solution caused by parathyroid action, while it allows the retention of the slight increases of the calcium concentration effected by the presence of the gland substances. It thus seems possible that these experiments may contain the germ of a fresh aspect of the rickets problem, although it is realized that there is a very wide difference between

the conditions in the body and those in the experimental solutions described.

SUMMARY

In a system of the type described there is some evidence to suggest the following conclusions:

1. Ultra-violet light and parathyroid substance both exert their action through the cholesterol fats in the solution; thyroid substance does not do so.

2. Parathyroid substance increases the calcium content of the solution on the alkaline side of pH 7.4. An increase in the acidity causes a decrease in the calcium content. These changes are not observed after exposure to ultra-violet light, with the exception of a slight but constant increase in the calcium content.

3. Thyroid substance increases the acidity of the solution and also its calcium content. The former effect is neutralized by the action of ultra-violet light.

This investigation was carried out under the Foulerton Committee of the Royal Society.

BIBLIOGRAPHY

1. Grant, J. H. B. and Gates, F. L.: J. General Physiol. (N. Y.), 1924, **6**, 635.
2. Windaus. Quoted by Dyke, S. C.: Quart. J. M. (Oxford), 1924, **18**, 77.
3. Bergstrand, H.: Acta Medica Scandinav. (Stockholm), 1921, **53**, 644.
4. Pappenheimer, A. M. and Minor, J.: J. Med. Research (Bost.), 1921, **43**, 391.
5. Ritter, C.: Frankfurt. Ztschr. f. Path. (Wiesb.), 1920, **24**, 137.
6. Hartwich, A.: Virchow's Arch. f. Path. u. Physiol. (Berl.), 1922, **236**, 61.
7. Luce, E. M.: J. Path. & Bacteriol. (Edinb.), 1923, **26**, 200.
8. Ghiron, V.: "L'Importanza delle Paratiroidi," Rome, 1924.
9. Falta, W.: "Endocrine Diseases." Transl. M. K. Meyer, 3rd Edn., London, 1923.
10. Korenchevsky, V.: J. Path. & Bacteriol., 1922, **25**, 366.
11. Collip, J. B. and Leitch, D. B.: Canad. M. Ass. J. (Montreal), 1925, **15**, 59.
12. Turpin, R. A.: "La Tétanie Infantile," Paris, 1925.

STUDIES ON VIGOR. XII. THYROID ADMINISTRATION IN SENILITY*

R. G. HOSKINS

From the Department of Physiology, The Ohio State University
COLUMBUS

That the thyroid gland shares in the bodily deterioration of old age is generally believed and the belief is supported by the frequent finding of sclerosis and atrophy in the thyroids of elderly people. That uncompensated thyroid deficiency may play a causal role in the senile picture is suggested by several facts. The symptoms of thyroid deficiency and the manifestations of old age have in common such features as lack of general vigor, dry and scanty hair, dry skin of lowered vitality, dislike of cold weather and decreased mental initiative. In cases of pathologically early senility (progeria) morphological evidence of thyroid deficiency has been reported. Claims, too, have been made that in man amelioration of the common manifestations of old age has been secured by the administration of thyroid substance.

So far as the signs of old age are concerned, the evidence is ambiguous. They might be due in greater or less degree to thyroid changes or merely to deterioration in the body cells themselves. The degenerative changes in the thyroid gland might be merely a part of the general picture of bodily deterioration having no primary significance.

Granting that certain elderly subjects do react favorably to thyroid treatment, the question arises whether such instances are not merely those of thyroid deficiency contracted earlier in life and carried over, unrecognized, into old age. That a considerable number of cases of this sort might be expected to exist is altogether probable in view of the frequency with which hypothyroidism is overlooked, even by good clinicians, both in youthful and adult subjects. A person reaching old age with a pre-existing thyroid deficiency would be likely to manifest certain signs of this in addition to any depression that might

*Aided by a grant from the Bache Fund.

occur in bodily functions not conditioned by a thyroid factor. On this hypothesis certain subjects might be expected to react favorably to thyroid treatment and others not. It might well be that this therapeutic test would be the only feasible method of detecting thyroid deficiency in the presence of other confusing manifestations of senility.

Whether or not thyroid deficiency is a direct factor in bringing about the manifestations of old age, the possibility that thyroid medication might be beneficial remains open. The impression that this material has a general "tonic" effect is fairly widespread, though its possibilities and limitations are still to be systematically determined. Kerr, Hosford and Shepardson (1926), for example, have recently reiterated the belief, based on several years of clinical experience, that the non-specific stimulating effect of thyroid substance is frequently of value. Other experienced clinicians, on the other hand, have little confidence in thyroid substance as a medicament except in cases of genuine hypothyroidism.

The problem is one that would seem to lend itself better to laboratory than to clinical investigation. So far as the evidence goes it indicates that spontaneous hypothyroidism is rare in experimental animals. Any improvement in the well-being of such animals, therefore, would not be accountable for as amelioration of signs of persistance of pre-senile hypothyroidism.

The revolving cage method is particularly well adapted to an investigation of this problem. Prolonged records of the spontaneous activity of hundreds of rats in our laboratory has shown that this is a sensitive test of the animal's condition. Perhaps the most striking contrast between a young adult and a senile rat is in their respective degrees of spontaneous activity. In our experience healthy males in their most active period average 5000 to 15,000 cage revolutions (yards) a day, whereas old animals may go for days at a time without making 10 revolutions. This is true of animals that, upon casual inspection, seem healthy and vigorous. They are quick and show strong defensive movements and apparently are capable of a great deal more activity than is ordinarily manifested.

METHOD

This report is based on 11 animals to which desiccated thy-

roid substance (Armour's) was fed for varying periods and in varying dosages. Six of the animals were of Wistar Institute stock and five were a hybrid strain of Wistar and wild Norway stock secured from the experimental laboratory of Swift & Co., of Chicago. Four of the animals had been castrated. All were males. Data as to age were not available except for animals No. 585 and No. 879, the ages of which were respectively 12 and 15 months. The others, judged by weight, condition of the hair and activity levels, ranged from one and one-half to two years or more of age.

The animals were kept in revolving cages of the type previously described (Durrant, 1925) and daily activity was taken as the criterion of results.

The dosage of thyroid substance had to be determined empirically. It ranged from 0.1 grain (6.5 mgm.) every other day to 1 grain (65 mgm.) six times a week over periods of from 4 to 26 days. The rats preferred the thyroid substance to their ordinary food, hence no special measures had to be adopted to insure its consumption. With the smaller dosages, however, as a practical means of handling the material it was powdered and mixed in fresh dough made up of some of the ingredients of the standard food mixture (whole wheat flour, milk powder and casein) and fed in pellets containing the requisite amount of thyroid.

RESULTS

In the lower ranges of dosage no effect was secured and in the upper ranges a distinct depressing influence was seen. With no dosage or interval of feeding was any significant beneficial effect detected.

The results of the experiments are set forth in the accompanying table. The daily activity in terms of cage revolutions was determined for 20 days preceding the thyroid feeding. This averaged 1062 turns per day. During the feeding period the average was reduced to 741 and during the 20 days following the feeding period it increased to 928 revolutions. The total amount of gland substance fed ranged from 2 to 13 grains, the average being 9.3 grains. Inspection of the table shows that in all but two cases the average activity was lowered during the thyroid period and in most cases some depression was carried

over into the post-feeding period. In the two instances in which the activity ranged higher during the feeding period the augmentation was well within the range of spontaneous variability in experiments of this type. Similarly, in two instances in the post-feeding period there seemed to be a beneficial after-effect, but this was too slight in magnitude in case of animal No. 3172

TABLE

Effects of Thyroid Feeding on Activity of Rats.

Animal No.	Weights		Average Daily Activity						Total Dosage in Grains
	A. Before Feeding	B. After Feeding	Preliminary Period	No. Days	Thyroid Feeding Period	No. Days	Post-Thyroid Period	No. Days	
10*	400	393	1364	20	106	12	710	20	3.5
114*	221	202	541	20	400	26	451	20	2.8
123*	286	284	2371	20	1345	4	2324	20	2.0
585*	240	293	1296	20	1389	26	696	20	3.0
696	333	310	8	20	4	17	3	20	13.0
879	450	464	944	20	601	17	762	20	13.0
3128	392	400	855	20	359	17	382	20	13.0
3129	363	370	748	20	544	17	484	20	13.0
3130	322	330	2268	20	2557	17	1797	20	13.0
3131	290	280	59	20	2	17	922	20	13.0
3072	390	440	1263	20	842	17	1671	20	13.0
Average....	335	342	1065	20	741	17	928	20	9.3

*Castrated previous to the feeding experiments.

to be regarded as significant. Animal No. 3131 averaged 922 revolutions daily after thyroid treatment as against 59 before and 2 during the feeding period. Since, however, this result was not confirmed in four other closely similar cases, and since occasional "sporadic" instances of such changes in activity are seen in untreated animals, the result in the one case is not regarded as significant.

SUMMARY

Eleven senile albino rats, kept in recording activity cages, were fed desiccated thyroid substance over periods of 4 to 26 days.

No beneficial effect as indicated by increase of spontaneous

activity was seen, except in one instance, and this is interpreted as probably accidental.

The series, as a whole, showed depressed activity both during and after the feeding period.

BIBLIOGRAPHY

Durrant, E. P.: 1925. This Journal, **9**, 221-228.
Kerr, W. J., Hosford, G. N. and Shepardson, H. C.: 1926. This Journal, **10**, 126-144.

STUDIES ON VIGOR. XIII. EFFECT OF EARLY CASTRATION ON THE VOLUNTARY ACTIVITY OF MALE ALBINO RATS

HOWARD M. GANS

From the Department of Physiology, The Ohio State University
COLUMBUS

Earlier studies in this laboratory (Hoskins, 1925) showed that animals deprived of their testes after puberty suffered approximately five-fold decrement of their spontaneous activity. Studies of the age factor in this phenomenon were planned some three years ago, when it was first noted. Subsequent studies have shown that the effect of castration is much more marked in rats with a normally high activity level but usually can be demonstrated even when the activity of early adulthood is as low as two or three thousand cage revolutions a day. The effect is seen, also, when toward old age the activity is materially lessened, but still of fair degree.

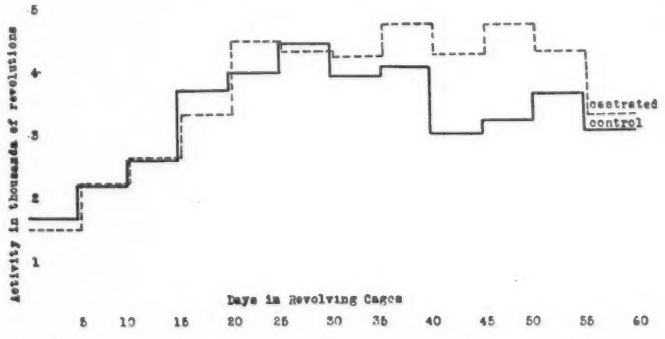


Fig. 1. Average five day activity of normal and castrated rats as manifested by turning revolving cages one foot in diameter.

This paper embodies the results secured when 25 rats were castrated between the ages of 1 and 11 days. Eighteen litter controls were also studied. After castration the animals were then returned to the cages and remained there until they were

TABLE 1

Average Daily Number of Revolutions of 25 Castrated Rats Tabulated Through 12 Consecutive Periods of 5 Days Each.

Animal	Group	Castrated at Age Days	In RC at Age Days	1	2	3	4	5	6	7	8	9	10	11	12
1	1	11	35	1483	1483	1492	1492	1817	1817	2356	2356	1783	1783	1672	1672
3	1	11	35	500	500	810	810	1237	1237	1605	1605	2540	2540	1184	1184
4	1	11	35	3520	3520	1469	1469	1781	1781	4232	4232	2920	2920	2669	2669
5	2	4	27	912	1124	2826	4030	2242	3096	3195	4150	3738	3236	4266	3374
8	2	10	27	456	1228	1328	3034	1850	1704	2146	3938	1516	1576	1280	1305
9	3	7	31	4476	4060	2420	3344	5476	2142	4608	3016	1020	2192	3704	4288
10	3	7	31	3116	3456	3286	5978	2224	5646	4474	4444	3844	3458	4262	4340
14	4	3	24	2620	3416	2444	3188	4614	6808	2178	2240	1372	2888	1792	2174
16	4	3	24	226	2654	2074	3978	8604	10356	6228	9302	8854	13358	8036	7642
18	5	1	23	1962			1150	2260	5548	4810	3774	2804	3016	5032	3934
19	5	1	23	1062	2190	3286	3206	9413	8914	6510	7182	3970	7310	9544	7778
23	6	3	28	34	134	962	1390	1782	2110	2986	2788	2760			
24	7	12	72	1470	2503	2109	2017	1965	2028	1679	1956				
25	7	12	72	494	1058	809	680	1070	930	1612	8059				
27	8	10	26	1498	2632	6984	11618	10042	7528	11052	14004	11628	14530	13500	11112
29	8	10	26	1812	3490	2598	5288	5954	5026	5050	3860	7060	4972	4724	5686
33	9	5	28	3782	6664	10058	7332	9678	10694	11390					
103	10	9	32	1004	1757	2607	2240	6814	6062	6438	6012	5840	6840	7794	
104	10	9	32	723	1331	1942	2006	6240	6982	5940	7536	7394	7770	6668	
109	10	9	32	428	1055	1539	2119	8288	4384	4458	2562	3040	2786	2678	
116	11	10	28	1308	1302	1464	1196	1054	1420	600	1458	856	522	470	860
117	11	10	28	896	1606	3490	7112	6196	1460	1430	2184	4614	5706	2930	5081
118	12	10	23	553	1230	1614	1462	2514	1474	1478	1486	1575	1472	1220	1380
119	12	10	28	1430	2168	2814	5093	5940	6420	6870	6902	2740	3420		
120	13	10	28	2700	2420	2378	2430	2868	2800	2378	3200	3268	2800	3100	2900
Average..		7.9	31	1538	2207	2635	3364	4476	4332	4228	4807	4283	4777	4326	3368

TABLE 2

Average Daily Number of Revolutions of 18 Controls Tabulated Through 12 Consecutive Periods of Five Days Each.

Animal	Group	In RC at Age Days	1	2	3	4	5	6	7	8	9	10	11	12
2	1	35	2893	2893	2494	2494	493	493	1281	1281	407	407	312	312
5	1	35	2890	5042	825	1943	2057	1676	2491	1836	1198	498	640	654
7	2	27	1278	3078	3668	2732	2550	2862	1888	1962	2116	3208	7664	3234
11	3	31	2374	2468	3238	10976	6426	3652	4194	6612	8368	9584	9438	8946
15	4	24	2706	3724	2900	1910	2398	1106	872	3234	3378	1544	1328	1322
17	5	23	2838	3284	4782	5140	6048	6444	6200	5960	3818	4836	8108	5716
20	6	28	484	1534	1510	2654	2372	3562	1478	2140	1485			
26	7	72	175	743	1764	2837	2169							
30	8	26	984	410	1196	5002	1810	1912	40	3972	10088	9568	7420	7496
32	9	28	4480	8190	9212	9664	6192	5072	8452					
105	10	32	428	1103	1976	3465	504	3292	3432	3292				
106	10	32	1838	2212	2901	2134	10790	15794	14094	15454				
107	10	32	1066	826	2186	1802	11200	15236	14988	12544				
111	11	28	416	1118	2020	5470	9678	6194	1988	1192	2876	3628	2950	2512
112	11	28	510	870	1212	3220	3278	4128	2378	2231	1787	2191	2777	2980
113	12	28	360	158	333	272	296	466	464	368	375	224	292	300
114	12	28	2064	2092	2536	1906	1932	1680	1864	1746	1836	1476	1696	1900
115	13	28	2820	2038	2477	2490	2064	2210	1626	2048	2046	1706	1422	2054
Average.....		31	1699	2321	2623	3728	4031	4463	3983	4122	3059	3239	3670	3116

weaned at about one month of age. At this time the control and experimental animals were placed in revolving cages, previously described (Durrant, 1925.) They remained in the recording cages for sixty days.

The results of the experiments are set forth in Tables 1 and 2 and in the accompanying graph. These need little comment. While the animals were in the activity cages, the activity was recorded daily, but in the tables average daily records of five days intervals were used. Within the limits of variability of the method, there was no difference between the activity of normal animals and those castrated at an early date.

No evidence has been secured as to what compensatory factors may have come into play to prevent the usual depressive effect of this operation.

I wish to acknowledge my indebtedness to Professor R. G. Hoskins for advice and suggestions in regard to this investigation.

BIBLIOGRAPHY

Durrant, E. P.: 1925. This Journal, **9**, 221-228.
Hoskins, R. G.: 1925. Am. J. Physiol. (Balt.), **72**, 324-330.

STUDIES ON VIGOR. EFFECT OF FRACTIONAL CASTRATION ON THE VOLUNTARY ACTIVITY OF MALE ALBINO RATS

HOWARD M. GANS

From the Department of Physiology, The Ohio State University
COLUMBUS

The effect of complete castration on the voluntary activity of the white rat depends upon the period of life at which the animal is castrated. If castration takes place after puberty, the castrated animal begins to lag behind the control. This occurs at about the twelfth day after castration. If the animal is castrated during the first two weeks of life there is apparently no effect on the voluntary activity of the animal.

In this work an attempt was made to study the effect of fractional castration on the voluntary activity. After typing

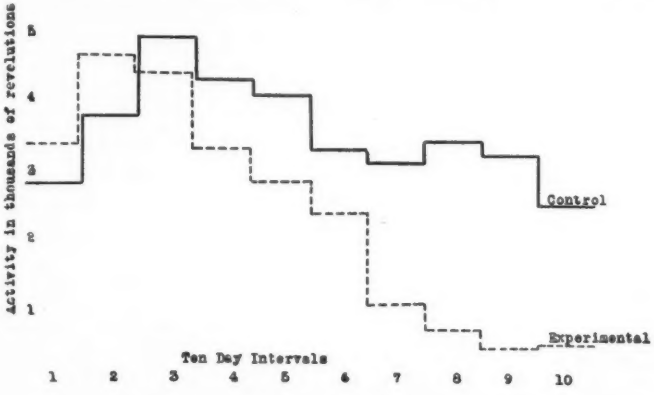


Fig. 1. Graphs of average activity of fractionally castrated animals and their controls tabulated through consecutive periods of ten days each.

the animals, unilateral castration was performed. The effects were observed for a period of twenty days. Then approximately one-half of the other testis was removed. The remaining part was removed in two steps at intervals of 20 days each.

The experiments have not yet been carried to adequate

length. Neither have enough animals been studied, nor have enough intermediate stages between half and complete castration been produced. Circumstances have arisen, however, that compel for the present a discontinuance of the research, hence the data so far secured are put on record for what they are worth.

TABLE 1

Average Daily Number of Revolutions of 18 Fractionally Castrated Rats Tabulated Through 10 Consecutive Periods of 10 Days Each.

Animal	1	2	3	4	5	6	7	8	9	10
30	2563	6720	7273	5844	3838	1775	476	137	201	140
5	2966	5403	6727	3766	2772	1345	627	364	727	230
56	3746	2415	2794	2560	5548	175	14	198	310	319
1	4492	6005	4386	9260	2017	40	22	168	464	
90	4322	8805	2046	1307	1170	897	1182	1334	855	1125
6	4210	5798	8550	6704	1086	1682	600	510	404	512
142	1286	2666	1838	3998	1774	1478	2426	1604	726	538
138	4208	3996	4688	1436	2394	3802	3490	1420	1010	2462
2	6125	5605	2308	4160	1690	624	398	126	348	220
32	5256	3772	2492	1926	1535	476	512	522	1030	428
3	6200	5006	4294	3860	4208	2176	188	426	506	630
142	1104	1418	1398	2476	2874	1592	2132	1718	550	62
56	2550	4124	4650	1890	2610	2936	2848	1754	654	242
46	3256	2990	4940	2445	2438	1892	1660	575	1024	762
90	2734	5054	7926	825	2308	1866	1510	1462	1018	964
137	1308	3550	4156	2268	4912	2508	1164	1230	332	924
106	2184	4614	5706	2930	5081	13156	1486	1486	630	506
68	4674	7170	5000	3840	5164	3196	1078	630	392	868
Average.....	3510	4725	4509	3416	2968	2312	1212	870	621	625
% deviation from controls.....	19.8	20.9	10.0	22.7	29.7	32.9	62.3	75.6	81.5	76.4

Period 1 Typing period.
" 2-4 One testis removed.
" 4-6 One and one-half testes removed.
" 6-8 One and three-fourths testes removed.
" 8-10, Inc. Both testes removed.

Several factors make a statistical study of this character difficult. Castration affects the voluntary activity of the rat to varying degree in different strains and even in different

members of a given litter. Thus the effect is quite marked in the case of the Wistar rat, while the Swift animal, Wistar-Norway hybrid, is much less affected. In the latter the fall in activity is rather slow and never attains as low a level as in the case of the castrated Wistar animal.

The accompanying tables and figure show the results obtained. It will be observed that before the operation the average activity of the experimental group was 19.8% higher than that of the control. Removal of one testis resulted in a reduction of activity from the original level to 10.9% higher than

TABLE 2

Average Daily Number of Revolutions of 15 Controls Tabulated Through 10 Consecutive Periods of 10 Days Each.

Animal	1	2	3	4	5	6	7	8	9	10
18	3635	4832	3845	2823	9831	4043	4600	4716	2962	1681
34	2522	3207	8775	3805	3570	4709	3909	2226	1932	2347
33	3762	5870	6783	6688	1788	1156	2053	2260	2809	3425
112	4129	4793	4046	3160	3989	4146	2015	2815	2821	3094
64	3 64	4337	5674	11962	8475	5185	4602	3442	3683	3361
11	4042	4566	2516	5546	4730	3250	3634	3692	2872	2758
106	606	3490	7112	6196	1460	1430	2184	4614	5706	2930
139	3656	4376	7262	5886	7068	6570	6158	2854	1844	3716
10	2758	1802	2708	1884	1614	1740	1212	1252	1190	
135	1857	4239	4350	2247	1144	1384	1540	1764	1176	1462
90	2170	2348	2124	1490	4862	3066	3250	4494	6726	4936
106	4804	7974	9087	5120	6362	4742	3452	5550	3774	2442
81	1006	1642	1790	1498	2396	2934	1976	2322	2756	3308
5	2088	3726		5896	4246	4246	5206	7480	8284	1152
113	1638	3392	4070	3075	2838	3124	2520	2646	1938	3194
Average.....	2929	3908	5010	4418	4224	3448	3220	3575	3362	2653

that of the control for a period of twenty days. After the second operation, in which half of the remaining testis was removed, the activity dropped to 26.2% less than the control level. During the third twenty-day period where one and three-fourths testes were removed, the activity dropped to 47.6% below the control level. After the complete removal of both testes the

average activity observed for a period of thirty days was 78.8% less than that of the level of the controls.

SUMMARY

A study of the effect of fractional castration of the voluntary activity of the rat was made. It is shown that fractional castration conditions the activity of the animal. The fall in activity after removal of one testis was slight. The most marked changes were observed after removal of the last fraction of the second testis.

I wish to acknowledge my indebtedness to Professor R. G. Hoskins for advice and suggestions in regard to this investigation.

Abstract Department

Changes in inorganic constituents of blood in suprarenalectomized cats and rabbits. Baumann (E. J.) & Kurland (S.), J. Biol. Chem. (N. Y.), 1927, **71**, 281; Abst. J. Am. M. Ass. **88**, 1034.

In the experiments done by Baumann and Kurland, evidence did not point to an alkalosis as one of the consequences of suprarenalectomy. Suprarenalectomy does cause a fall in plasma sodium and chlorides. In the cat, a rise of plasma potassium, magnesium and, occasionally, calcium has been found. In a few other conditions in which suprarenal injury occurs, it has been found that a decrease in sodium and chloride content of plasma also occurs.

New research on the action of extracts of the adrenal gland on muscular fatigue (Nouvelles recherches, sur l'action des extraits de capsules surrenales sur les muscles fatigues). Ferreira de Mira (M.), Compt. rend. Soc. de biol. (Par.), 1926, **95**, 1284-1285.

Fresh extracts of mammalian adrenals were injected into the dorsal lymph sac of frogs whose gastrocnemius muscles had been fatigued. The result—a remarkable recovery of the contractility of those muscles—appeared to be due to epinephrin because the latter alone was just as effective. Solutions (2 cc.) of 1:100,000 of epinephrin caused greater amplitude of the contraction and postponed the onset of fatigue considerably.—J. I. Evans.

Blood calcium and adrenalin action (Blutkalk und Adrenalin wirkung). Frisch (F.) & Fried (E.), Wien. Klin. Wchnschr., 1926, **39**, 1389-1391.

The authors compare the blood calcium concentration to the hemodynamic effects of epinephrine injections. In the human subject conditions with low blood calcium make for a more powerful blood pressure rise from epinephrine than in instances of normal or high blood calcium. This inverse proportionality is taken to denote a dependent relationship between sympathetic irritability and blood calcium concentrations.—A. L. Tatum.

Influence of yohimbine on splanchnic nerve action and of nicotine on adrenal secretion. Houssay (B. A.) & Molinelli (E. A.), Rev Soc. Argent. Biol. (Bs. Aires), 1926, **2**, 26-32. Compt. rend. Soc. de biol. (Par.), 1926, **95**, 808.

In dogs deprived of their adrenals the inversion of the pressor

vascular response to splanchnic stimulation, produced by the action of previous injections of yohimbine, was still retained. The hypertensor effect of extracts of glands of the scorpion (*Buthus quinquestriatus*) persisted unaltered. By the method of suprarenal-jugular anastomosis in dogs it was observed that an intravenous injection of yohimbine did not produce adrenal discharge. The hypertensor effect of splanchnic stimulation and injection of nicotine gradually became less and then ceased, although a slight increase of adrenal secretion that raised the arterial pressure and contracted the spleen of the recipient dog was still produced. The adrenal-secretory effect of the splanchnic was more resistent than the vaso-constrictor effect. —Author's Abst.

The blood supply and weight of the adrenal glands and their relation to body surface and body weight. Houssay (B. A.) & Molinelli (E. A.), Rev. Soc. Argent. Biol. (Bs. Aires), 1926, **2**, 117-129.

In 100 male dogs (weight 10 to 38 kg.) the blood supply of the left adrenal was proportional to the body weight. The average amount of blood passing through the left adrenal was 0.345 cc. per kg. per minute. The weight of the left adrenal was not proportional to the body weight, but approximately to the body surface. A similar relation is shown by the data of Langlois for dogs and by that of Donaldson for male rats. In female rats (Donaldson) the adrenal weight is more nearly related to body weight. The significance of these results is discussed.—Author's Abst.

Blood sugar, glucose consumption and formation of glycogen after removal of suprarenals. Pico Estrada (O.), Semana méd. (Bs. Aires), 1926, **33**, 1653; Abs. J. Am. M. Ass., **88**, 1041.

In experiments on dogs by Pico Estrada the blood sugar fell after removal of the suprarenals. At death, hepatic and cardiac glycogen had diminished considerably; the decrease in muscular glycogen was also pronounced, but not so great. After intravenous injection of dextrose there was little change in the hepatic glycogen, and the glycogen in the muscles and heart increased only slightly. In suprarenalectomized animals, the blood in the femoral vein contains as much glucose as does the arterial blood. Suprarenalectomy seems to bring about a disturbance in the metabolism of the carbohydrates, decreasing the glycogen function of the liver.

Ovarian hormone in the blood (Untersuchungen über das Ovarialhormon im Blute gravider und nichtgravider). Fels (E.), Klin. Wchnschr. (Berl.), 1926, **5**, 2349.

A considerable series of tests of blood serum from non-pregnant and pregnant women were made in spayed mice, using the

oestrous reaction of the vagina as a criterion of the presence of ovarian hormone. Serum taken during different stages of the menstrual cycle was uniformly negative. Negative results were obtained during the first few months of gestation. Later in pregnancy the majority of tests were positive. Apparently a conclusive demonstration of the presence of this hormone in the blood during the latter half of gestation.—E. Allen.

Precocity of endocrine origin (Beitrag zur endokrin bedingten Frühreife—Interrenal-genitales Syndrom). Herschmann (H.), & Neurath (R.), Wien. klin. Wchnschr., 1927, **40**, 277-279.

A description is given of a 11-year-old girl with the stature of about 16 years. There is a history of lues in her mother and mother's mother. Development was normal until three years of age, when there appeared a remarkable acceleration in growth, pubic hairs, enlargement of the clitoris and a hesitancy in the gait which became worse after 4½ years of age. When nearly 5 years old she began to have fever, night sweats, and a cough. At 5 years of age, when admitted to the out-patient department, she was lively and talkative, slender in build, 117 cm. high, with a reach of 113 cm.; 63 cm. in sitting height, 51.5 cm. in head circumference, and 21.5 kg. in weight. She had a cerebellar-ataxic gait, positive Rhomberg, exaggerated tendon reflexes in lower extremities with indications of petellar clonus on both sides. No visceral abnormalities were found. Mons veneris and labia majora were covered with hair. The clitoris was 2.5 cm. long. Inner genitalia were not palpable. There was no abnormal hair development in other parts of body. Mammary glands were not developed. Urine was normal. Wassermann was negative and X-rays of hand and head were negative. The present status of the child at 12 years of age: Strong and muscular; fatty deposit noticeable only on mons veneris; much hair on legs, especially below the knee; axillary and pubic hairs as in adult female; well developed mustache; teeth irregular and defective; height, 152 cm.; reach, 159 cm.; sitting height, 89 cm.; weight, 49.6 kg.; head circumference, 56 cm.; lower portion of the body was too short for upper portion; the larnyx was slightly prominent and the voice was coarse; there were no visceral abnormalities; nervous status was negative except for a positive Chvostek's sign and slight exophthalmus; all evidence of ataxia was absent; the intelligence was that of a 7-year-old child; there was a negative Wassermann and the X-rays of the head were negative; mammary glands were not developed; the clitoris was 4 cm. long and the vagina 9 cm. long; a mass about the size of a cherry (probably uterus) was palpable through the rectum; there was a body about the size of a bean in the region of the left ovary and on the right was found a smooth, almond-shaped movable mass; no ligaments could be felt. Abderhalden's reactions were interpreted as

indicating defective hypophysis (both lobes), thymus, suprarenal cortex and ovary, but normal thyroid and pineal. The case is discussed especially from the point of view of suprarental cortex and gonad disturbances.—A. T. R.

Internal secretions of ovary: III. Effects of injection of oestrin during lactation. Parkes (A. S.) & Bellerby (C. W.), J. Physiol. (Lond.), 1927, **62**, 301.

A mouse suckling a litter of more than two does not come into oestrus (except for the post-partum period) during normal lactation. The corpora lutea of the post-partum ovulation are persistent and probably oestrus inhibiting. Injection of the oestrus producing hormone during lactation induced oestrus, at which copulation would take place. The amount required showed a close correlation with the number of young suckling. Where litters of 7 were suckling, as much as 10 mouse units of oestrin were required. When only 2 were suckling, oestrus was spontaneous. No pregnancy was observed to follow copulation at the induced oestrus period. Ovaries sectioned after copulation showed no young corpora lutea. It is concluded that ovulation did not occur during the artificial period. Mice ovariectomized early in lactation required only small amounts of oestrin (2 mouse units) to produce oestrus, whatever the size of the litter suckling, so the inhibitory effect of lactation is set up via the ovary and probably via the persistent corpus luteum. The dosage of oestrin required to over-ride the corpora lutea of lactation is greater than that required to over-ride the corpora lutea of pregnancy.—M. O. Lee.

The effect of the testis on metabolism in the chicken (L'influence du testicle sur le metabolisme chez les Gallinaces). Szuman (J. G.), Compt. rend, Acad. de sci. (Par.), 1926, **183**, 1053-1055.

The amount of food ingested, the amount of excreta and the nitrogen balance per day was studied in normal chickens, capons, and capons with testicular grafts. The amount of food voluntarily eaten and the amount of excreta given off by the capon were about 50 per cent that by the normal male. In capons with testis grafts the amount of food eaten and the amount of excreta were practically the same as in the normal male. Even with testis grafts amounting to only one-tenth of the average testicle, no differences were found. Cocks with one testicle removed gave the same results. Data as to the minimum maintenance level of nitrogen intake were not obtained.—M. O. Lee.

The unity of multiplicity of the autacoids of the posterior lobe of the pituitary gland. Draper (W. B.), Am. J. Physiol. (Balt.), 1927, **80**, 90-99.

Abel's conclusion that the various pharmacological effects of

pituitary extract are due to a single substance is challenged. It was found that the pressor and oxytocic activities have a widely differing distribution during normal butyl alcohol extraction. The results of Dudley and of Schlapp are thus confirmed. The renal activity followed closely the pressor activity during normal butyl alcohol extraction. The separation by extraction of the oxytocic activity from the renal and pressor activities is explained by assuming that the hormone responsible for the oxytocic activity is chemically separate from that responsible for the pressor and renal activities. The data obtained do not warrant a conclusion as to whether the pressor and renal activities are due to one or more than one substance. A bladder fistula method of assaying the renal activity of posterior lobe extracts is described. This method, although time-consuming and possessing a rather large margin of error, may, in the absence of a better one, be of some use in standardizing this activity.—R. G. H.

Structure of the pars intermedia of the hypophysis in man (Sulla struttura della pars intermedia dell'Hypophysis cerebri dell' uomo). Guizzetti (P.), Arch. d. Biologia normale (Fiernze), 1927, **80**, 665-735.

The hypophysial fissure remains open in man until about 16 years. Tubular glands are regularly present at birth. They secrete sero-albuminous materials, beginning in fetal life and ending at about the time of puberty. Evaginations of the hypophysial fissure arise from the ventral wall of the fissure at its cephalic extremity and penetrate deeply into the transition zone from the pars intermedia to the tongue-like process. They are special formations, of a different nature than the rest of the fissure and largely coalesce to form the cysts of the pars intermedia. The epithelium of the evaginations begins to differentiate toward the end of the first year of life. Two varieties of cells are described. The evaginations secrete substances which, by their histo-chemical reactions, must be classed with the mucins. This secretion begins only after one year from birth and continues thereafter, more or less constantly throughout life. The cysts of the pars intermedia are derived from three sources: from segmentation of the fissure; from the tubular glands; from the evaginations of the fissure. The cysts derived from the last two sources present different morphological characters by which it is easy to distinguish one from the other.—W. J. Atwell.

Studies on the anterior lobe of the pituitary body. Johns (W. S.), O'Mulvenny (O.), Potts (E. B.) & Laughton (N. B.), Am. J. Physiol. (Balt.), 1927, **80**, 100-106.

Extracts of the anterior lobe of the pituitary body of the ox, when injected into healthy adult dogs (number not stated), caused

hyperglycemia, polyuria and glycosuria. Renewal of the treatment gave polyria and glycosuria, but no hyperglycemia. The hyperglycemia is ascribed to increased glycogenolysis in the liver, since no glycogen was found in the liver of the treated animals. It is deduced that the threshold value of the kidney for glucose was lowered as a result of the administration of the extracts. The action of extracts on blood pressure and uterine strips was not similar to the action of "pituitrin." Extracts of liver and muscle made by the same process as the extracts of the anterior lobe of the pituitary body, failed to give similar results when administered to healthy adult dogs.—R. G. H.

The induction of precocious sexual maturity by pituitary homeotransplants. Smith (P. E.), Am. J. Physiol. (Balt.), 1927, **80**, 114-125.

It was found that daily homoplastic transplants of the pituitary from the adult, given intramuscularly, induced sexual maturity in the female rat as early as the weaning date (22 days of age), this transcending all normal variability. Animals which are but 14 days of age when treatment is begun mature sexually in from 8 to 10 days; when the treatment is begun at the weaning date they mature in five or six days. The opposite response of the sex apparatus results from pituitary ablation before sexual maturity, the complete establishment of the vaginal canal being delayed and the genital system remaining undeveloped. The anterior pituitary component of the transplant only, is essential for the induction of premature sexual maturity, the posterior lobe of the pituitary neither hindering nor aiding in the response. No stimulus to the development of the uterus or vagina of the immature ovariectomized rat is given by these transplants. The invariable and rapid maturity which is induced by daily pituitary transplants speaks against the view of those who maintain that hypophysectomy does not interfere with sexual development or function, and indicates an important hypophyseal-gonadal interrelationship.—Author's Abst.

Treatment of diabetic coma.—Chabanier (H), Lebert, Lobo-Onell & Lumiere. Presse méd. (Par.), 1927, **35**, 83; Abst. J. Am. M. Ass. **88**, 1040.

The authors consider the two phases in diabetes, the precomatose and that of established or "confirmed" coma. In the first phase acidosis is due exclusively to excessive formation of acetone bodies. In the other phase there is retention of acetone in the kidney, due to disturbed function of that organ. The phenomenon is revealed by deficient micturition associated with low concentration of urea in the urine and hyperazotemia. While insulin alone suffices in the precomatose phase, in comatose conditions diuretics and cardiac stimulants should be given in addition. Of 28 cases of diabetic

coma, only two resisted insulin treatment. Nine patients died, in spite of the subsidence of acetonemia and recovery from coma.

Artificial hibernation in the woodchuck (Arctomys Monax). Dworkin (S.) & Finney (W. H.), Am. J. Physiol. (Balt.), 1927, **80**, 75-81.

When a woodchuck is given an amount of insulin sufficient to produce profound hypoglycemia, it loses its power of temperature control. If it then be placed in an environment even moderately cool, it passes into a state of artificial hibernation. The characteristics presented by an animal in this condition are: the woodchuck becomes poikilothermic; it is unable to shiver or execute spontaneous movements; consciousness is lost, and the animal is insensible to painful stimulation; the convulsions associated with insulin hypoglycemia do not occur; the metabolic rate is greatly decreased. The state of torpor thus induced can be prolonged by the administration of insulin at intervals. The injection of glucose terminates this condition. Shivering begins almost immediately, the temperature rises at a rapid, though variable, rate, and the animal returns to normal.—Authors' Abst.

Activation of insulin (Über Aktivierung von Insulin). Glaser (E.) & Halpern (G.), Biochem. Ztschr. (Berl.), 1926, **177**, 196-205; Abst. Physiol. Absts., **12**, 41.

The oxidase obtained from eosinophile granules of the blood and kinase obtained from the small intestine function as activators of insulin, whilst peroxidase from bone marrow and liver aldehydase are inactive. Irreversible inactivation of insulin is observed by treating with aluminium hydroxide. Alteration of pH does not markedly affect insulin action. Tyrosinase and peroxidase of horseradish have no effect, but yeast juice boiled for 8 hours has a marked activating effect on insulin.

Insulin treatment. Holzer (H.) & Klein (O.), Deutsches Archiv. für klinische Medizin (Leipz.), 1926, **153**, 129; Abst. J. Am. M. Ass., **88**, 1042.

Holzer and Klein had good results in treatment of grave diabetes with large doses of insulin (100 units or more) and of carbohydrates (from 120 to 200 gm.). The patients improved rapidly and the insulin dose was soon reduced. The authors attribute the improvement to a formation of carbohydrate reserves and suggest the preventitive use of the treatment in patients with grave and moderately grave diabetes. It would be necessary to repeat the course several times a year.

Diabetes. One thousand cases. John (H. J.), Arch. Int. Med. (Chicago), 1927, **39**, 67; Abst. J. Am. M. Ass., **88**, 1032.

One thousand cases of diabetes are analyzed by John. The incidence of syphilis in this series was 2.6%. There was an hereditary history of diabetes in 4.6%, and a familial history in 5.1%. The highest blood sugar level on admission was 908 mgm. per hundred cubic centimeters. Blood sugar figures as high as 310 mgm. per hundred cubic centimeters were encountered without glycosuria. The diabetic renal threshold was high in many cases. The general belief that insulin once used must always be continued is shown to be fallacious by the cases in which good progress has followed the discontinuance of insulin. The mortality rate in 35 operations on diabetic patients in this series was 20%. By the exclusion of 4 cases in which death was due to septicemia, which was present at the time of operation, or to inoperable carcinoma, the mortality rate is reduced to 8.5%. There were 28 cases of diabetic coma. The blood sugar in these cases ranged from 200 to 810 mgm. per hundred cubic centimeters; the plasma acetone from 0 to 3 plus, and the plasma carbon dioxide from 44.3 to 9.9 mm. of pressure. The higher figures in the last instance were due to the administration of insulin previous to the carbon dioxide determination.

Physiological ideas on vagotonia (pancreas and vagal tonus). Santenoise, Tr. Reunion Neurologique, Paris, June, 1926; Arch. Neurol. & Psychiat. (Chicago), 1927, **17**, 271.

Vagotonic persons have a remarkable tolerance for carbohydrates; on the other hand, those with hypotonia have a low tolerance. In patients in whom vagotonia fluctuates, there are parallel fluctuations in carbohydrate tolerance. The injection of insulin seems to have a stimulating effect on the pneumogastric, analogous to the action of epinephrin on the sympathetic system. Following injections of insulin there is slowing of the heart, exaggeration of respiratory arrhythmia, increase in the amplitude of contraction due to the lengthening of the diastolic phase and exaggeration of the oculocardiac reflex. This vagotonic action of insulin is immediate and is not modified by raising the sugar in the blood by injection of glucose, showing that insulin is a specific excitant for the parasympathetic system. In experimental animals the vagal tonus seems to run parallel with the size and weight of the pancreas, animals having large glands being largely vagotonic. In the circulating blood there is a hormone that exerts this vagotonic action; the serum coming from the pancreatic vein is extremely active. Blood drawn two hours after pancreatectomy is inactive.

Simplification of the dietetic treatment of diabetes mellitus. Winn (R. C.), Med. J. Australia (Sydney), 1927, **1**, 321-325.

An attempt has been made to simplify the details of the dietetic treatment without sacrificing any of its principles. Rest to the islands of Langerhans continues to be the essential principle and this can best be secured by a moderate reduction in the diet, without "insulin" in the majority of cases and with "insulin" if sufficient food to do light work cannot be supplied otherwise. The Allen method is ineffective in emaciated patients, unnecessary in others and because of starvation (and consequent lowered resistance to infection) obnoxious and harmful in all. Though the Allen method has been superseded, unnecessary detail associated with it has been retained by many. In the method here described the patient is examined once a week and increases of 200 calories are made in the diet if the urine is "sugar-free." By varying combinations of three "diet groups" (of 500, 600 and 900 calories), it is possible to supply completed diets ranging from 1,000 calories to any limit, with rises of one hundred up to 2,000. Just as it is the custom in lists of vegetables and fruits to strike averages for the carbohydrate content, so for meat and fish average figures have been used. Only a few exceptions and alternatives have been listed.—Author's Abst.

Use of parathyroid extract in hemorrhage. Gordon (B.) & Cantarow (A.), J. Am. M. Ass. (Chicago), 1927, **88**, 1301-1302; Abst. A. M. A.

In the prevention and treatment of 347 cases of hemorrhage arising from various sources, the authors employed parathyroid extract, from 10 to 15 units every thirty to thirty-six hours, except in a few instances in which from 15 to 20 units were administered every twenty to twenty-four hours. The plan of treatment was to continue the injections until cessation of hemorrhage occurred, and then to administer one dose after thirty-six hours. So far as possible other treatment was discontinued. The series includes hemorrhage from the following sources: the respiratory system, the majority of which were instances of pulmonary bleeding; the gastro-intestinal and genito-urinary tracts, and operative incisions in various parts. The extract was also administered to patients with jaundice, and in other conditions in which the clotting time of the blood was prolonged. Cessation occurred in 304 patients, following one or more transient increases in the calcium content of the circulating blood. The most favorable results followed the administration of from 10 to 15 units every thirty-six hours for one to three doses. As a preoperative measure in jaundice, it reduced the coagulation time to within normal limits and apparently prevented hemorrhage. The unfavorable results occurred when over-

dosage and prolonged administration were employed. In addition, unfavorable results occurred in blood dyscrasia (puerperal hemorrhage and hemorrhagic disease of the new-born) irrespective of the size and number of doses, apparently because of certain local changes in the tissues. As compared with the common experiences with oral and intravenous administration of calcium the results are more dependable, and furthermore gastric irritation and other untoward effects are avoided. The hormone was found to be of special value in patients recovering from surgical operations who were unable to tolerate oral therapy. The use of parathyroid extract is suggested as a means for controlling hemorrhage because it effectively mobilizes calcium salt, which is normally stored in the body and which is necessary for clotting.

Tetany and syphilis of the parathyroids. Langeron (L.) et al., Presse méd. (Par.), 1927, **35**, 81; Abst. J. Am. M. Ass., **88**, 1040.

In the authors' case, a man aged 47, was admitted to the hospital for digestive disorders followed by decrease in calcium and an increase in the alkali reserve. Necropsy revealed, among other lesions, gummas in the lungs and syphilitic sclerosis of the parathyroids. The changes in the liver and in the kidneys were insignificant. The corpus striatum appeared almost intact. Lesions of the parathyroid could be responsible for alkalosis and hypocalcemia, which, in turn, might induce neuromuscular hyperexcitability and tetany. Derangement of gastric secretion from chronic alcoholism appeared as a contributing factor in this case.

Occurrence of parathyroids on anterior surface of thyroid gland. Millzner (R. J.), J. Am. M. Ass. (Chicago), 1927, **88**, 1053-1055; Abst. A. M. A.

During a period of six months, 162 thyroidectomies were performed at the University of California hospital. In twenty of these cases one parathyroid was removed, and in one case two parathyroids were removed. The author gives assurance that all but six of the twenty-one parathyroids were checked and proved by microscropic study of a small fragment. The six that were not checked were typical in every respect, and grossly looked exactly like those that were checked. In none of the cases did the patients develop any clinical signs of tetany. Studies are now being carried on with autopsy material. In approximately 10% of normal thyroids, one or more parathyroids lie on the anterior surface of the gland. In 30%, one or more parathyroids are present on the lateral surfaces of the gland. The clinical significance of this work is self-evident. With modified technic, leaving the lateral and part of the anterior capsule of the thyroid, approximately two-thirds of the parathyroids now removed are saved. Parathyroids may be recognized at operation by their characteristic appearance and reimplanted.

Histologic studies on endocrines of chickens deprived of ultraviolet light. I. Parathyroids. Nonidez (J. F.) & Goodale (H. D.), Am. J. Anat. (Phila.), 1927, **38**, 319; Abst. J. Am. M. Ass., **88**, 1031.

Nonidez and Goodale noted that the combined effect of lack of direct sunlight and a ration poor in antirachitic vitamin on the parathyroids of growing chicks is expressed in enlargement of these glands. Microscopic examination of the glands show that this enlargement is due to increase in cell size (hypertrophy), and increase in number of the epithelial cells (hyperplasia). The phase of hypertrophy and hyperplasia is followed by a phase of regression during which the epithelial cords appear shrunken. Shrinkage of the cords may coincide with hyperplasia of the stroma. Local degenerative changes, such as production of keratin and mucous degeneration, were present in the regressed glands of some of the chickens examined. It is suggested that these phenomena are not the immediate result of the treatment, but are caused by some other factors of unknown nature, and that degenerative tendencies are probably favored by the abnormal condition of the glands. The parathyroids of chickens that are deprived of ultraviolet rays for five weeks and subsequently exposed to direct sunlight are much smaller than the corresponding organs in younger birds not receiving exposure. Microscopic examinations show that the decrease in volume of the glands is due to a decrease in cell size, resulting in considerable crowding of the epithelial cells. Pressure atrophy also occurs in some of the glands

Goiter prevention. McCarrison (R.), Brit. M. J. (Lond), 1927, **1**, 94; Abst. J. Am. M. Ass., **88**, 1037.

McCarrison gives additional evidence bearing on the importance of providing a chemically and bacteriologically pure water supply, if goiter is to be eradicated. Iodine, he says, has nothing to do with the matter. Goiter, which had been endemic in Sanawar for seventy years, has now disappeared; and its disappearance has been due to the introduction of a new and protected water supply. Its eradication within the short space of three years is, McCarrison says, unparalleled in the history of goiter prophylaxis.

Changes in the thymus and thyroid in endemic goiter. Messerli (F. M.) & Coulaud (E.), Ann. de l'Inst. Pasteur (Par.), 1926, **40**, 952; Abst. J. Am. M. Ass., **88**, 1039.

Messerli and Coulaud's research was conducted on rats. In Paris, where endemic goiter does not exist, the size of the animals' thyroid was half that of rats in Strasbourg and Lausanne, where a few cases of endemic goiter are observed. In Zurich, where endemic goiter is frequent, the thyroid of the animals was three or four

times as large as that of rats in Paris. In all instances, the volume of the thymus paralleled that of the thyroid. This accords with Wagner von Jauregg's report that thymus extracts associated with thyroid extracts are effectual in preventive treatment of endemic goiter and of cretinism. It is probable that in countries with endemic goiter the thymus persists longer in man.

Treatment of obstinate obesity. Shepardson (H. C.) & Allen (R. E.), California and Western Medicine (San Francisco), 1927, **26**, 33.

In two cases of obesity the basal metabolism, as determined by the ordinary methods, was within normal limits, yet it was apparent that the actual metabolism was decidedly abnormal. In each instance the diet was reduced to a level considerably below the basal requirement without impairment of health, and a definite loss of weight resulted beyond which further reduction was unobtainable by dietary restriction alone. Thyroid extract was then used, as a general stimulant to metabolism rather than to supplement a thyroid deficiency, which neither of these cases showed. This addition of the thyroid extract resulted in further loss of weight and permitted an increase in the diet to a point where moderate exercise produced no untoward effect, such as might have been produced on the previous extremely low caloric intake. This form of treatment is not advocated in all cases of obesity. It was employed in the study of more difficult cases only when they could be kept under close observation. The grave danger of any form of reduction regimé which produces a too rapid loss of weight is emphasized.—M. O. Lee.

The course of hyperthyroidism under iodine medication. Starr (P.), Arch. Int. Med. (Chicago), 1927, **39**, 520-535.

The course of hyperthyroidism under iodine medication is characterized by remission and recurrence during the administration of iodine and by a reaction, which may be extreme, after the iodine is discontinued; hence, the prolonged treatment of patients who have hyperthyroidism with iodine in dosage sufficient to produce these effects is without final benefit.—Author's Abst.